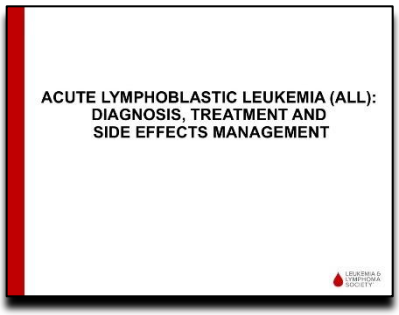
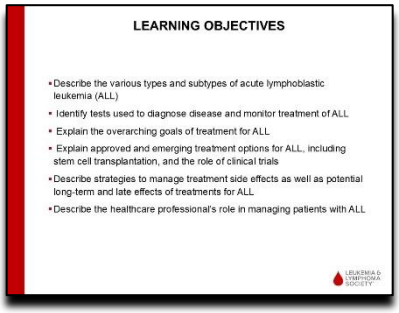


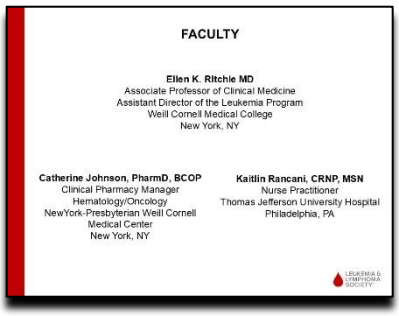
Slide 1: Acute Lymphoblastic Leukemia: Diagnosis, Treatment, and Side Effect Management

Hello everyone. On behalf of The Leukemia & Lymphoma Society thank you for sharing your time with us for this continuing education program on Acute Lymphoblastic Leukemia**:** Diagnosis, Treatment, and Side Effect Management.



Slide 2: Learning Objective

The learning objectives for this program are listed on this slide.

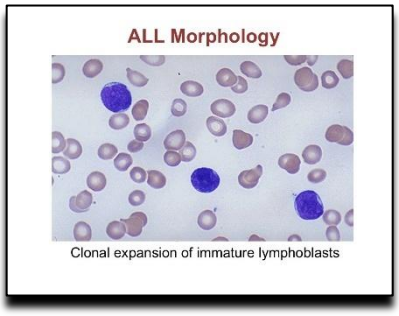


Slide 3: Faculty

We're fortunate to have as our presenters, Dr. Ellen Ritchie, a leading expert in ALL, Dr. Catherine Johnson, a clinical pharmacist, and Ms. Kaitlin Rancani, a nurse practitioner. We appreciate their dedication and their commitment to caring for patients living with blood cancer.

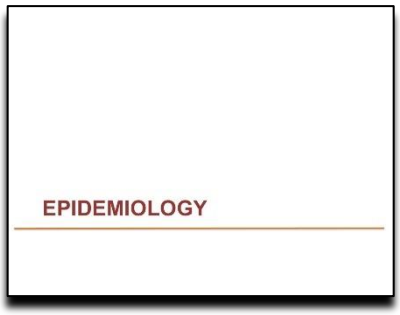
Dr. Ritchie is Associate Professor of Clinical Medicine, and Associate Director of the Leukemia Program, at Weill Cornell Medical College in NY, NY. Dr. Johnson is Clinical Pharmacy Manager, Hematology/Oncology, Weill Cornell Medical Center, NY Presbyterian Hospital, in New York. Ms. Rancani is a Nurse Practitioner at Thomas Jefferson University Hospital, in Philadelphia, Pennsylvania.

Dr. Ritchie, Dr. Johnson, and Nurse Practitioner Rancani, I am now privileged to turn the program over to you.



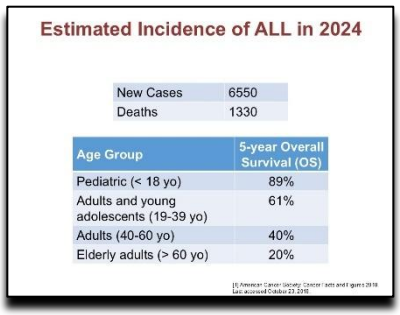
Slide 4: ALL Morphology

Dr. Ritchie: So ALL morphology, and this is a picture of what an ALL cell looks like, which is this sort of larger than a red cell, with a cell that's filled with this powerhouse nucleus, that drives this malignancy to be the dominant feature in a person's blood. So, it's a clonal expansion of immature lymphoblasts that end up taking over your bone marrow; and subsequently, all of your blood cells really become the



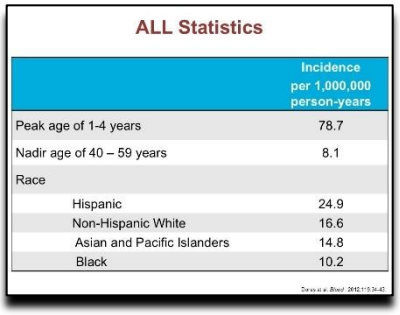
Slide 5: Epidemiology

We're going to talk first a little bit about the epidemiology.



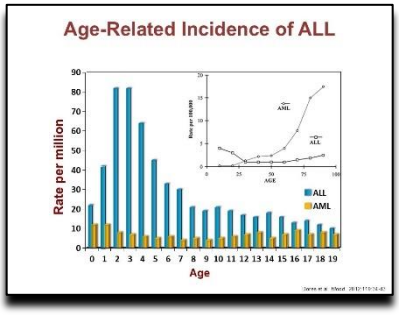
Slide 6: Estimated Incidence of ALL in 2024

And this the incidence of ALL in 2024. It's not a lot of cases, 6,550; but for the number of cases, there are a lot of deaths, 1,330. And as you can see, that the overall survivals differ significantly at 5 years from age group. So the pediatric age group has the best 5-year overall survival at 89%. But as the population ages, 5-year overall survival really declines. As early as being a young adult, which starts at age 19, up to age almost 40, the overall survival decreases to 61%. But in adults 40 to 60, 40%; and elderly adults have a very poor overall survival



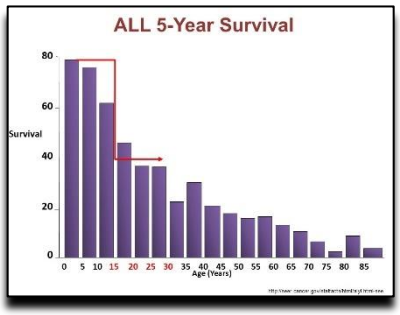
Slide 7: ALL Statistics

So, SEER data, which was collected from 2001 to 2007, looks at the age-adjusted rates of the US population for people getting ALL. The peak incidence of this disease is really in children age 1 to 4. And as you can see, the incidence declines as patients age. That, the nadir age of 40 to 59 years, the incidence is 8.1 per million person years. Interestingly, there's an increased risk in patients who are Hispanic as compared to other races who are vulnerable to developing ALL.



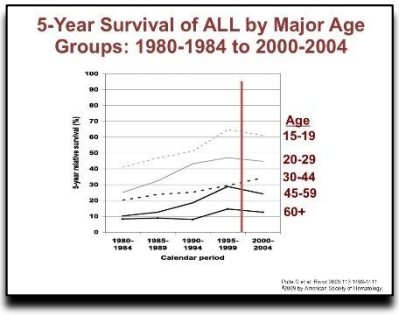
Slide 8: Age-Related Incidence of ALL

The age-related incidence, you can see, again, graphically where the peak incidence is really in children and that it declines as people ages. And as you can see, there's another sort of little peak as patients age into their 60s.



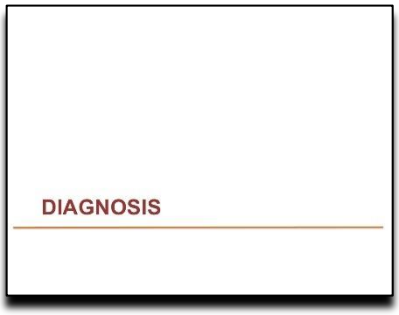
Slide 9: ALL 5-Year Survival

The overall 5-year survival also is best in children that receive generally a pediatric style regimen where their overall survival has reached almost 80 to 90%. But this declines with age again. And as you can see in the elderly population has a very poor overall survival.



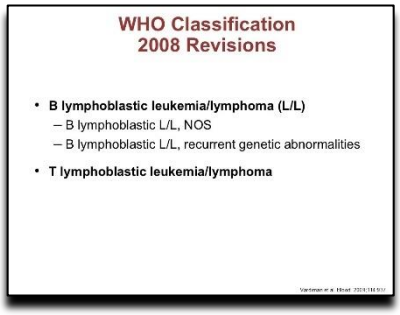
Slide 10: 5-Year Survival of ALL by Major Age Groups: 1980-1984 to 2000-2004

The 5-year survival, as you can see again, graphically by major age group, declines really with age. And over 60, the overall survival with this disease is relatively dismal.



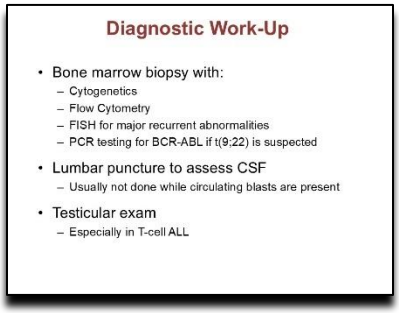
Slide 11: Diagnosis

Diagnosis



Slide 12: WHO Classification 2008 Revisions

The WHO Classification has some 2008 revisions. The — ALL is really divided into two categories, B-cell leukemia/lymphoma versus T-cell lymphoblastic leukemia/lymphoma. There is B-cell lymphoma that has a lot of recurrent genetic abnormalities; those included genetic alterations such as *BCR-ABL*, *MLL*, *ETV6-RUNX1*, hyper- and hypo-diploidy, and others. These genetic abnormalities are important in determining prognosis and potentially the best treatment for the patient.

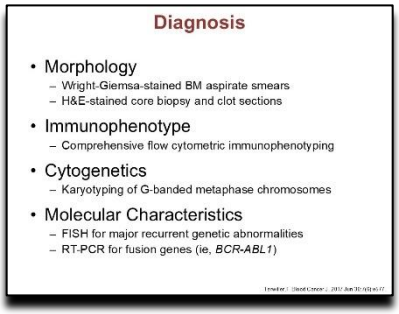


Slide 13: Diagnostic Work-Up

Diagnostic workup is done with a bone marrow biopsy. So, anyone who we suspect has this disease ends up having a bone marrow biopsy where cytogenetics are sent. Flow cytometry, FISH for major recurrent genetic abnormalities, and PCR testing for *BCR-ABL* if a *BCR-ABL* gene mutation is suspected.

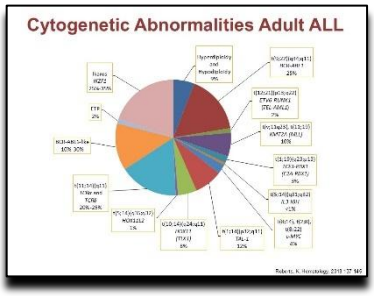
At diagnosis, it's also important to do a lumbar puncture, because this disease likes to live in the central nervous system. We try not to do this while circulating blasts are present in the peripheral blood. We generally like to wait until the blasts have disappeared with initial chemotherapy, so there's no contamination of this particular assessment when we're trying to determine whether there is disease.

The testicular exam is also important in males. Generally, we don't know at the outset whether the patient is a T- or B-ALL, but T-ALL is more likely to have testicular abnormalities; but it's really important that this be a part of your initial assessment of a patient.



Slide 14: Diagnosis

Morphology. We look in the Pathology Department. Stains, the slides looking for the characteristic findings of an ALL cell. It's usually a core biopsy which is done, and clot sections. The immunophenotype is determined by flow cytometry, and that's looking at what the markers are in the outside of a leukemia cell. Again, that helps potentially in determining treatment options later on. Cytogenetics are done where karyotyping G-banded metaphase chromosomes is done, looking for the recurrent genetic abnormalities that we might see in patients with ALL. And if we suspect that there is a particular genetic abnormality, like *BCR-ABL*, we do FISH for that as well as sending for RT-PCR for fusion chains such as *BCR-ABL*.

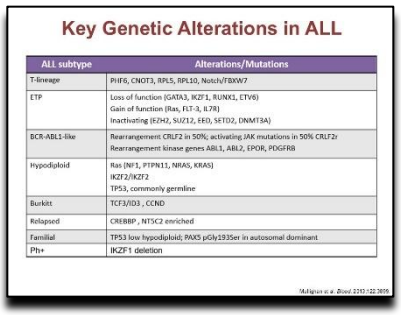


Slide 15: Cytogenetic Abnormalities Adult ALL

The cytogenetic abnormalities in ALL: there are many of them. As you can see, *BCR-ABL*, which is a common abnormality in ALL patients, really represents about 25% of patients who have this disease. Other poor prognostic mutations like the *KMT2A* mutation is present in about 10%, and the 11;14 TCRA-α and TCR-δ, 20 to 25% of patients.

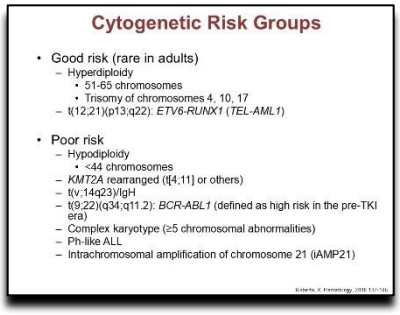
There's a *BCR-ABL*-like ALL which is not positive for ALL but positive for, for genetic abnormalities that make it look like BCR-ABL. And that's in 10 to 30% of patients. And

IKAROS, which is a, kind of a poor *Kzf1*, a relatively poor prognosis, a molecular abnormality. Again, it is present in about 25 to 35% of patients.



Slide 16: Key Genetic Alterations in ALL

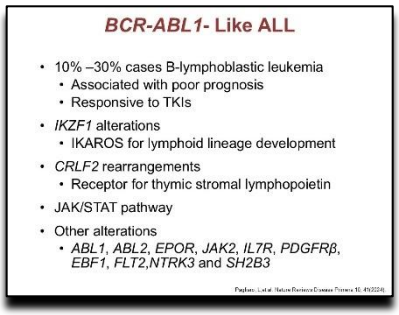
Dr. Ritchie: So, key genetic alterations in ALL, depend, to some degree, on lineage or T-lineage. There are different alterations than for B-lineage. But as you can see, there are a number of different genetic abnormalities that occur in different subtypes, really, of ALL. So, the T lineage, ALL has things like PHF6 and Notch mutations. But you can see that the different B-cell subtypes have very different molecular characteristics.



Slide 17: Cytogenetic Risk Groups

Cytogenetic risk groups, there are good-risk ALLs. That includes hyperdiploidy, where there are too many chromosomes. That can be either trisomy is a different chromosomes or just too many that are numerically there.

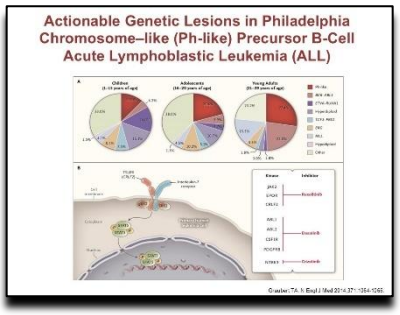
There is also particular subtype 12;21 translocation, which is a good-risk ALL. These good risk ALLs are more concentrated in younger patients, and they are less common as patients age. What becomes more common as patients age are poor-risk mutations, which we mentioned before: the hypodiploidy, the *KMT2A* rearrangement, the *BCR-ABL* chromosome, anything that's complex with more than 5 chromosome abnormalities, this Philadelphia chromosome-like ALL, and any intrachromosomal amplifications of chromosome 21.



Slide 18: *BCR-ABL1*-Like ALL

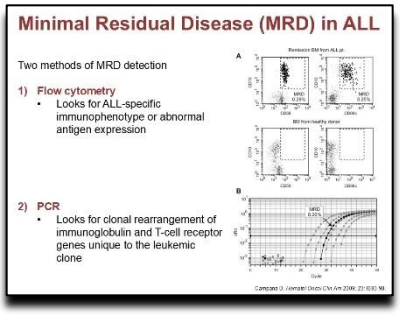
So, *BCR-ABL*-like ALLs are, represent about 10 to 30% of B-ALL cases. Again, like Philadelphia chromosome-positive, it's associated with a poor prognosis. But they also are responsive to the drugs that we use to treat *BCR-ABL*-positive disease, which are the TKIs.

The IKAROS alterations are also associated with the *BCR-ABL*-like ALLs, and always represent a poor prognosis. *CRLF2* rearrangements are also associated with *BCR-ABL*-like ALL, and the JAK/STAT pathway alterations are associated with *BCR-ABL* type, ALL; again, offering the possibility for more targeted therapies. There are other alterations which also can be common in this *BCR-ABL*-like ALL, which needs to be thought of any time that we're looking at a disease that looks like *BCR-ABL*, because it could be either *BCR-ABL*-positive or *BCR-ABL*-like.



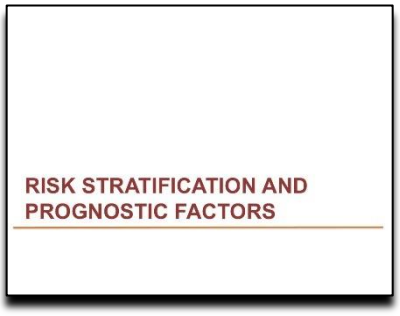
Slide 19: Actionable Genetic Lesions in Ph-like Precursor B-Cell ALL

So, again, this is a picture, really, of actionable genetic mutations in this Philadelphia chromosome-like precursor B-ALL. And as you can see, because of the variety of mutations which are associated with this *BCR-ABL*-like disease, there are more drugs that are available to treat this type of disease. So, those patients who have certain mutations in *JAK2* or *EPOR* or *CRLF2* might respond to ruxolitinib as a drug that could be added to that regimen. Again, and as sort an *ABL* gene mutations will respond to dasatinib; and *NTRK3* to crizotinib, which is actually a lung cancer drug that is active in ALL patients.



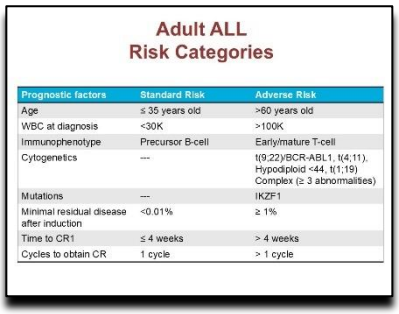
Slide 20: Minimal Residual Disease (MRD) in ALL

It's important when we assess response to patients who have received therapy for ALL that we look as to how much disease or whether there is any disease left at all when we give them treatment. And what we're looking for is MRD, which is minimal residual disease, and there are two common methods of MRD detection. One is flow cytometry, which is looking for ALL-specific immunophenotypes or abnormal antigen expression on the outside of cells. The other method which is used is PCR, which is looking for a clonal rearrangement of immunoglobulin and T cell receptor genes which are unique to the leukemic clone. The superiority of either is really something that is debated, but both methods are used to look for MRD in patients who have ALL.



Slide 21: Risk Stratification and Prognostic Factors

We're going to look now to risk stratification and prognostic factors.

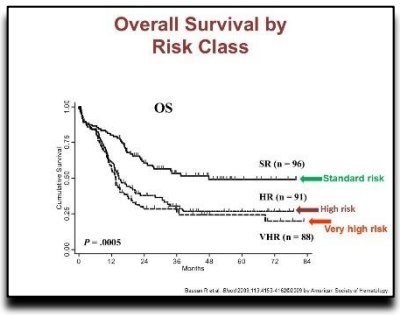


Slide 22: Adult ALL Risk Categories

And these are adult ALL sort of risk links. We look at age so that under 35 is the standard-risk disease and is a better prognostic category at the age of diagnosis. Over 60 really gives an adverse risk. What the white blood cell count is at presentation is important in assessing risk, so under 30 000 is a lot better than over 100 000 with a lot of proliferative disease. Immunophenotypes are important, precursor B-ALL is more of a standard-risk disease, as opposed to early or mature cell T-cell ALL, which has an adverse risk. Cytogenetically, the hypodiploid and the 12;21 translocation give a more favorable risk as opposed to Philadelphia chromosome, Philadelphia chromosome-like hypodiploid and complex karyotype.

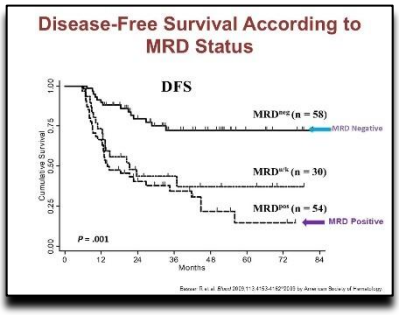
Mutations. The IKAROS mutation is a poor prognosis mutation and should be looked for in patients at the time of diagnosis of their disease. Minimal residual disease after the initial chemotherapy given for ALL is very important. So, if the minimal residual disease after that initial chemotherapy is less than 0.01%, that's a favorable risk factor. If it's greater than 1%, patients need to be treated as if they have residual disease.

The time to obtaining a complete response, if it's less than 4 weeks, that's a better prognostic factor than if it's greater than 4 weeks. And the cycles needed to obtain a complete response: if 1 cycle is needed, that's superior to more than 1 cycle of therapy.



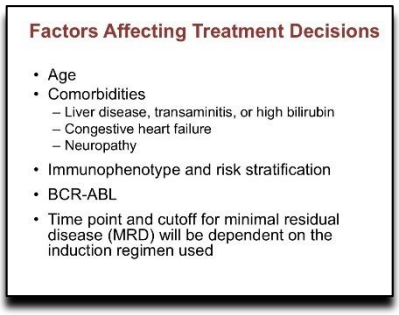
Slide 23: Overall Survival by Risk Class

So, the overall survival by risk class is, is pretty dramatic. So, standard-risk disease, overall survival at 84 months is really around 50%. However, if you have high-risk or very-high-risk disease, that falls really to the 25 or less than 25% range. And this data is from Bassan et al in Blood 2009. It's very dramatic.



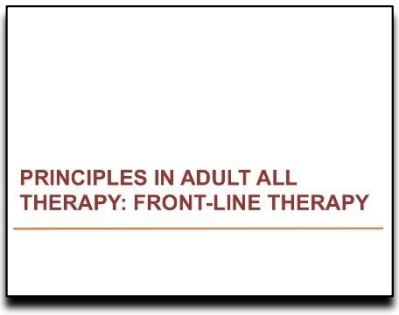
Slide 24: Disease-Free Survival (DFS) According to MRD Status

This again is another slide looking at disease-free survival according to risk class showing that MRD-negative disease is far superior to NR, the survival of patients who have MRD-positive disease. So, it's really, really important in determining how you're going to manage these patients in looking at MRD after the first cycle of chemotherapy.



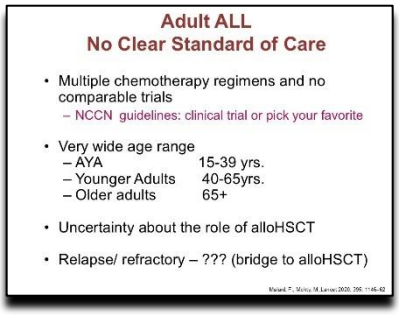
Slide 25: Factors Affecting Treatment Decisions

Factors affecting treatment decisions are really: age, comorbidities that the patient may have, liver disease, congestive heart failure, or neuropathy at the time of diagnosis. We look at immunophenotype and the risk stratification of those patients to determine what treatment we think might be the most effective for a given patient. Whether they're *BCR-ABL*-positive is a very important initial step to know in making a treatment decision for patients. And the timepoint and cutoff for minimal residual disease assessment is generally dependent on the induction regimen used. So, depending on induction regimen, we decide to look at whether the patient is MRD-positive and make decisions about ongoing treatment based on that assessment.



Slide 26: Principles In Adult ALL Therapy: Front-Line Therapy

So, we're going to talk now about principles in adult ALL therapy and in, what frontline therapy might consist of.

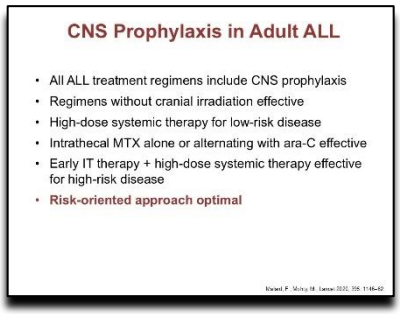


Slide 27: Adult ALL No Clear Standard of Care

So, for adult ALL, there's actually no clear standard of care. There are multiple chemotherapy regimens, and no comparable trials looking at these different chemotherapy regimens and which one might be the most effective for what kind of patient.

So, the NCCN guidelines really recommend a clinical trial or sort of pick your favorite among these different regimens that are available to treat adult ALL. There's a very wide range of ages of older people who have this disease; and that also informs, really, our treatments decision-making. An adolescent, young adult — we think of more as trying to treat like a pediatric style patient. So that's really an adolescent. Patients who are younger adults, 40 to 65, we really have to look at different patient factors, comorbidities, and their overall health, in determining what the best regimen might be. And older adults over 65, the standard of care is really not defined. These patients are often frail, with other organ abnormalities; and, again, clinical trial is favored. But if that's not available, choosing amongst the mini regimens that, more intensive or less intensive that are available to treat the older patient.

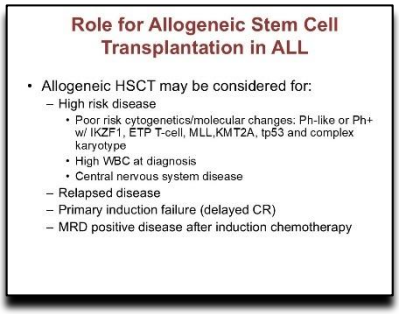
There's now uncertainty about the role of allo stem cell transplant. When do we step in with that, given, especially, the introduction of CAR-Ts into our treatment algorithms? And relapsed/refractory disease, how do we bridge these patients and get them to allotransplant? That's the patient population where there will be no cure without allotransplantation.



Slide 28: Central Nervous System (CNS) Prophylaxis in Adult ALL

CNS prophylaxis is mandatory in all adults with ALL. Regimens that do not contain granule irradiation are effective, and we can use high-dose systemic therapy for low-risk disease.

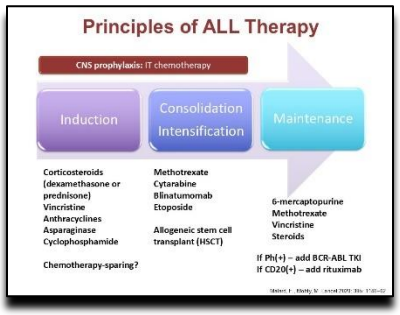
Or intrathecal methotrexate alone or alternating with Ara-C (cytarabine; Cytosar®) are effective. Early intrathecal therapy and high-dose systemic therapy are effective for high-risk disease. And early IT therapy should be started in these patients. And a risk-oriented approach based on whether CNS disease is present at diagnosis or not is optimal.



Slide 29: Role for Allogeneic Stem Cell Transplantation in ALL

Dr. Ritchie: So, allogeneic stem cell transplant may be considered at the outset for high-risk disease, which is the Ph-like or Ph-positive disease with IKAROS mutations. ETP Ts cell ALL, *MLL*-positive, or *KMT2A*-positive ALL. Our patients with familial *TP53* or complex karyotype.

Patients who have a high white blood cell count at diagnosis also are patients who you would think potentially may be candidates for a stem cell transplant. Anyone who presents with central nervous system disease at the time of their diagnosis is high risk and may be a candidate for stem cell transplant. All patients with relapsed disease are candidates for stem cell transplant. And anyone who has primary induction failure or a delayed complete remission is a candidate for stem cell transplant. And any patient who is MRD-positive at the, after induction chemotherapy, is a candidate for stem cell transplant.



Slide 30: Principles of ALL Therapy

Catherine Johnson, PharmD, BCOP: Thanks, Dr. Ritchie. So, as Dr. Ritchie mentioned, in the NCCN guidelines there are tons of different regimens to pick from. And when a provider might look at a protocol, it may seem complicated at first because of the number of regimens, the medications, the cycles, the schedules, and things like that. But really, the principles of ALL therapy can be summed up into these four parts. The first is going to be induction chemotherapy in which patients get multimodal chemotherapy for the most part, but the ultimate goal is to induce a remission. This is defined as having like 5% leukemic blasts in the blood and bone marrow, no extramedullary disease, which means no disease outside of the bone marrow, and usually count recovery.

Corticosteroids and vincristine are included in almost all regimens with the cytotoxic induction chemotherapy, whether the patient is 7 or 70 years old. Anthracyclines are selectively given to our fit patients who have a good ejection fraction, so these patients tend to be less than 60 years old. And, last but not least, asparaginase (Rylaze®), which is only given to our pediatric or young adolescent, young adult population, the AYA (adolescent and young adult) patients on pediatric-inspired regimens. And this is really true due to the side effect profile.

We'll talk about some induction chemotherapy examples in the upcoming slides. As newer drugs and studies are being introduced, there is potentially a role for chemo-sparing approaches, and Dr. Ritchie will talk about this more in depth in the upcoming slides. Once patients complete their induction and achieve remission, the next phase is consolidation or, in some protocols, it may be referred to as intensification. The goal of consolidation is to eliminate any potential residual disease and maintain the achieved remission, and you do this by giving additional chemotherapy, such as high-dose methotrexate or cytarabine (Cytosar®)-based regimens. We also see a role for blinatumomab (Blincyto®) being used in patients with or without minimal residual disease.

Specifically, consolidation does require a few cycles, so this spans over like a few months. For patients who can be cured through chemotherapy alone, they'll proceed to maintenance based on the protocol that they're on. But if they have to go through an allogeneic stem cell transplant — and those patients are the candidates that Dr. Ritchie spoke about in the previous slide — this may be done after a few cycles of consolidation, or maybe even immediately after induction for our high-risk patients.

So, maintenance, arguably, is the longest phase when it comes to ALL treatment; and this extends another 1 to 2 years of therapy. And this is, again, to minimize the risk of relapse at this point. But when you're looking at what drugs are being used, it's really just once-a-month infusions of vincristine, a few days of steroids, oral mercaptopurine (Purinethol®),

and weekly oral methotrexate. So really, the intensive chemotherapy portion is done at this point.

As Dr. Ritchie already highlighted, all ALL patients must receive CNS prophylaxis throughout these treatment phases, which is going to be the fourth part we were referring to. And this is going to help prevent and/or potentially treat CNS disease.

Slide 31: Role of Oncology Pharmacist

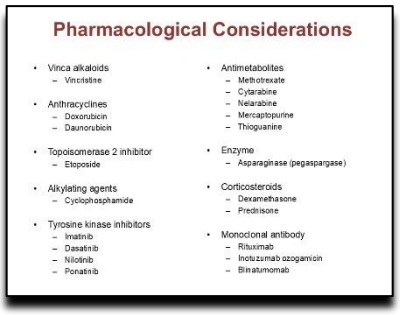
So, as the oncology pharmacist, we believe we have a huge role in treating ALL patients during all the phases of treatment; and we work alongside our physician colleagues, as well as other members of the care team, to make sure our patients are getting medications in both a safe and effective way.

Patients may encounter different types of pharmacists, whether it's in the hospital, in clinic, or even in the community setting. The oncology clinical pharmacist does help the oncologist select and individualize the correct chemo for the patients based on their age, organ function, underlying comorbidities, allergies, drug interactions with existing organ and future medications. And we are heavily involved in chemotherapy counseling and providing educational material to not only the patients, but also their caregivers. After starting treatment, the pharmacist is responsible for frequently and thoroughly reviewing the patients' medications to see if anything should be added, removed, or adjusted. We conduct toxicity and lab checks to see how well patients are tolerating chemotherapy and assess if we need to make any additional dose adjustments.

So pharmacists are not only responsible for optimizing chemotherapy but also any supportive care connected to the management of a newly diagnosed ALL patient, especially those who are receiving induction chemotherapy for the first time. This includes identifying the right preventative anti-infectives, adding medications to prevent nausea and vomiting, minimizing pain, and managing any other side effects that may come a patient's way.

Pharmacists have a key role in monitoring drug levels with certain medications to make sure, again, they're receiving the right and safe amount. And we might make antibiotic recommendations for you as well.

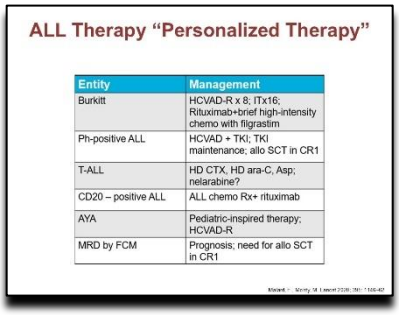
As patients become ready to be discharged from the hospital, oftentimes they leave with more medications than what they started with. So, it is critical for the pharmacist to help with that smooth transition to home. We assist the medical team in securing prior authorizations, addressing any barriers to adherence, review discharge medication lists, and again provide discharge counseling so it's absolutely clear what patients have to take when they go home.



Slide 32: Pharmacological Considerations

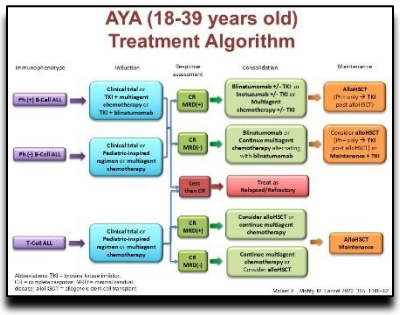
Traditionally, when we think of ALL management, we have used multimodal cytotoxic chemotherapy and steroids throughout treatment phases. However, we know that immunotherapy and oral targeted therapies have changed the game in ALL management.

In the past, being Philadelphia chromosome-positive, for example, was a poor-risk future; but now with the introduction of tyrosine kinase inhibitors targeting the BCR-ABL protein, patients have a much better prognosis. We add rituximab (Rituxan®) in patients who have CD20-positivity on their B cells. And blinatumomab (Blincyto®) and inotuzumab (ozogamycin; Besponsa®), for example, were first approved in the relapsed/refractory setting; but now we're finding a place in consolidation and even in select patients' up-front therapy as well. So, although we don't have time to go through every single medication used in ALL, we will highlight some of the more pertinent ones where pharmacists can play a huge role in dosing and side effect management.



Slide 33: ALL Therapy "Personalized Therapy"

Dr. Ritchie: There is sort of an attempt at a personalized therapy in patients with ALL, depending on the type of ALL they have and what markers they might have on the surface. So, for Burkitt-positive disease, we think about hyper-CVAD and potentially adding rituximab (Rituxan®) if there is a CD20-positivity. For Ph-positive ALL, we tend to use hyper-CVAD plus a TKI with TKI maintenance and, potentially, depending on risk, allo stem cell transplant in first remission. For T-ALL, we use high-dose Cytoxan® (cyclophosphamide), high-dose Ara-C (cytarabine; Cytosar®), and asparaginase (Rylaze®) plus or minus nelarabine (Arranon®), which has been shown in the pediatric setting to be highly effective in this population. Patients who are CD20-positive, we add Rituxan® (rituximab). Your very young adult disease, adolescent disease, we try and use pediatric-inspired therapy. Or if they're CD20-positive, hyper-CVAD plus Rituxan® (rituximab). And if they're MRD-positive, we think after their induction chemotherapy, we recognize early on that we need to go for a stem cell transplant.



Slide 34: AYA (18-39 Years Old) Treatment Algorithm

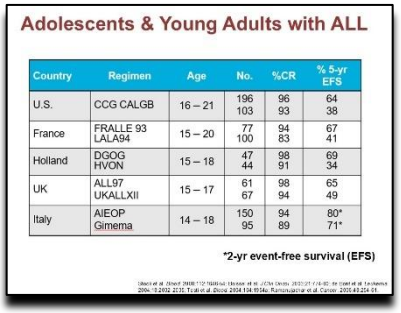
So, for the young population, this sort of adolescent, young adult population, this looks like a pretty complicated treatment algorithm. It depends really on whether you're Ph-positive or Ph-B-cell ALL-like positive, or you had T-ALL, as just sort of how we go forward and manage these patients.

If you're B-cell-positive ALL, we look for chemotherapy plus T-, TKI or maybe using up front a TKI plus blinatumomab (Blincyto®) as initial treatment in this patient population. For B-cell-like ALL, if possible, we like to put these patients on clinical trial, or we use a pediatric style regimen with multiagent chemotherapy to treat them more like the kids so their outcome would be better.

For T-ALL, we think also of a pediatric style regimen, maybe incorporating nelarabine (Arranon®), which has been effective in the pediatric setting or enrolling patients on a clinical trial.

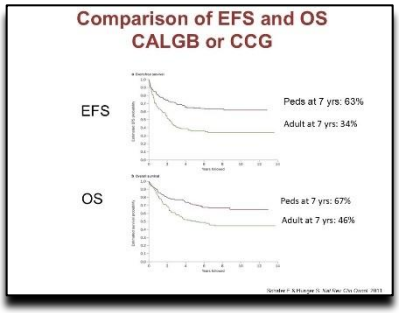
It's important at response assessment to determine what the next steps are. So after induction, we look to see, how well they have responded. You know, patients who have a CR but are MRD-positive, we need to go forward with either blinatumomab (Blincyto®) plus a TKI or inotuzumab (ozogamycin; Besponsa®) plus a TKI or multiagent chemotherapy plus a TKI in patients who are B-cell for Philadelphia chromosome-positive disease. And those patients will need to go for allo stem cell transplant for cure. Those patients who are MRD-negative, we can think about going forward with blinatumomab (Blincyto®) and TKI and to clean up whatever disease might be left and thinking about risk factors in determining whether they go for allo stem cell transplant.

If a patient is CR MRD-negative, we really look at those sort of other risk factors for poor prognosis to determine whether they need to go for transplant. If patients don't get a CR, they need to be treated as if they have relapsed or refractory disease. And in T-cell ALL, if you're MRD-positive, we need to go forward with multiagent chemotherapy and plan for stem cell transplant. If they're MRD-negative again, multiagent chemotherapy and looking carefully at those patients' other risk factors to determine whether or not they go for allo stem cell transplant or for maintenance.



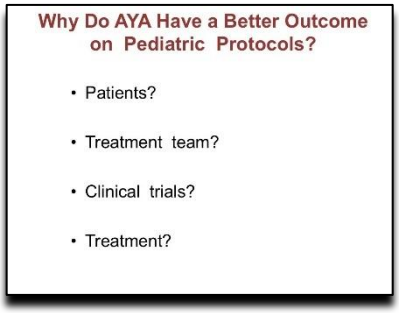
Slide 35: AYAs with ALL

There are many regimens for adolescents and young adults with ALL, many of them based on pediatric style regimens. And this is sort of comparing the 5-year survival, really, of a regular regimen, versus a pediatric style regimen. And this is looking at 2-year event-free survival and looking at sort of outcomes on cooperative group trials. It's sort of the C-, Children's Cancer Group and the Leukemia Group B studies. And you can see that the CR rates are generally high. But the 5-year survival is quite different, depending on whether or not you receive a pediatric style regimen versus a non-pediatric style regimen. And that our goal is really in these younger patients to try and incorporate the pediatric style regimen and schedule.



Slide 36: Comparison of EFS and OS CALGB or CCG

You can look here at the event-free survival and overall survival of patients on sort of CALGB-type protocols versus the Children's Oncology Group type of protocols. And you can see that event-free survival if at 14 years here is far superior in the peds-treated group as opposed to the CALGB-treated group, and that's true of overall survival as well.

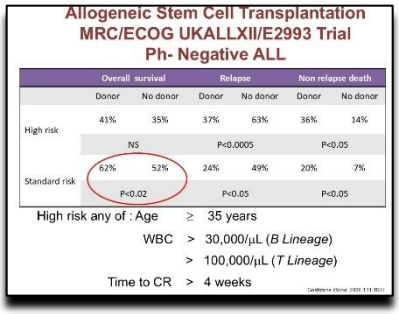


Slide 37: Why Do AYA Have a Better Outcome on Pediatric Protocols?

So, the question is, why do these young adults have such superior outcome on the pediatric protocol? And is it because of the way we have chosen patients to go on pediatric style protocols versus CALGB? Does the doctor really handpick these patients, and then that's been affecting the treatment outcome on cooperative group trials? Did it have anything to do with the treatment team? At places where there's large volumes of ALL patients treated, does it make a difference, as opposed to patients where they're very small volumes? Is the organization of different kinds of treatment teams: for example, the incorporation of a pharmacist into the main portion of the team and a social worker? Does that make a difference in the outcome of these patients?

Are they — the clinical trials themselves — what agents and the schedules included? Are patients adhering to the schedules? Sometimes with adult patients, we are less strict about timing of particular treatments, like their IT therapy or a particular treatment. If it falls on Christmas Day, we may, for example, delay that. Is that making a difference in the outcome of our patients? Or is it the treatment itself? Is it the agents that we've

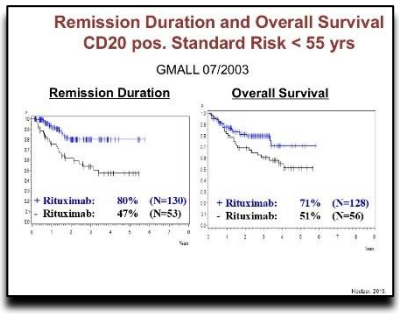
incorporated into the different protocols and the timing of when those agents appear that's making a difference in the overall survival of these patients?



Slide 38: AlloHSCT MRC/ECOG UKALLXII/E2993 Trial Ph- Negative ALL

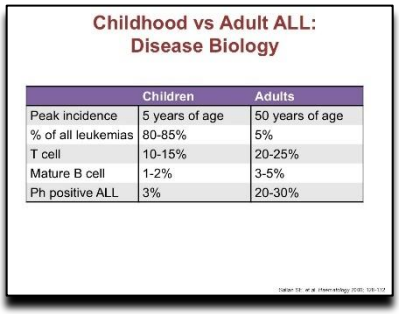
And looking at allogeneic stem cell transplant, it can be somewhat confusing in the sense that here is an MRC trial that was presented at the plenary session at, of ASH, you know, looking at sort of overall survival of patients who were transplanted with standard-risk disease, versus patients who were treated essentially with high-risk disease.

And, you can see that high-risk disease is really, barely sort of statistically significant. But there is no significance, sort of, in the overall survival of high-risk disease versus standard-risk disease, really, in patients who get allogeneic stem cell transplant on this MRC trial. So, who should get allogeneic stem cell transplant? Still a little bit confusing and up in the air.



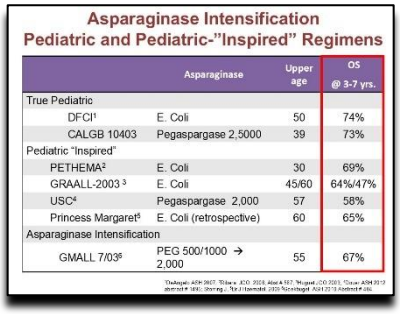
Slide 39: Remission Duration and OS CD20+ Standard Risk < 55 yrs

So, looking now at patients who are CD20-positive where we are incorporating rituximab (Rituxan®) into their treatment regimen, looking at standard-risk disease — those are patients under the age of 55 — the remission duration of patients who got rituximab (Rituxan®) was far superior to those who did not get rituximab (Rituxan®). Again, overall survival also was far superior in patients who got rituximab (Rituxan®) versus those who did not get rituximab (Rituxan®), suggestin g certainly in this patient population the choice of medications that patients get at the outset of their disease has a huge impact on their remission duration and overall survival. So these patients under 55 who get rituximab (Rituxan®), you certainly aren't going to think necessarily about sending them to allo stem cell transplant.



Slide 40: Childhood vs Adult ALL: Disease Biology

So childhood versus adult ALL. The sort of disease biology — in adults, T-cell is more prevalent than it is in children. Mature B-cell ALL is more prevalent by a little bit in adults versus children. But certainly Ph-positive ALL is much more prevalent in adults as opposed to children, which is a poorer-risk disease.

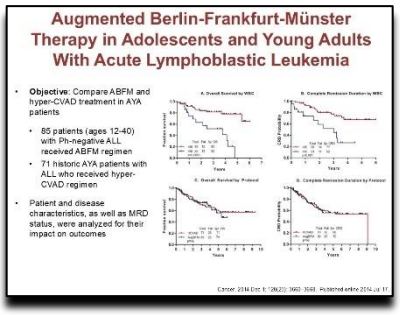


Slide 41: Asparaginase Intensification Pediatric and Pediatric-"Inspired" Regimens

So, asparaginase intensification is really the hallmark of pediatric and the pediatric-"inspired" regimens. So, giving higher doses of asparaginase (Rylaze®) seems to be what makes a real difference in the regimens that treat adults versus children, and, really, in improving potentially the outcome of children with ALL. So, looking at sort of the different types of asparaginase (Rylaze®) used, whether it's, *E. coli*-based asparaginase (Elspar®) or PEG-asparaginase (pegaspargase; Oncaspar®), and looking at sort of the upper age limits where these patients were treated.

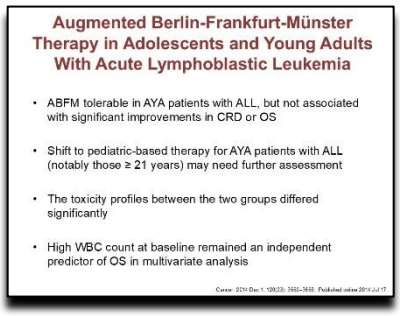
And you can see really the highest or the oldest patients that were treated with higher doses of asparaginase (Rylaze®), the upper age really was 60 years. And that the overall survival of patients who get these higher doses of asparaginase (Rylaze®) is far superior to those who don't get this higher dose of asparaginase (Rylaze®).

So, the asparaginase (Rylaze®) intensification is really, really important to the overall survival; and it may be this ingredient, so to speak, in the recipe for a childhood disease that really makes the difference in their better overall survival.



Slide 42: Augmented Berlin-Frankfurt-Münster Therapy in AYAs With ALL

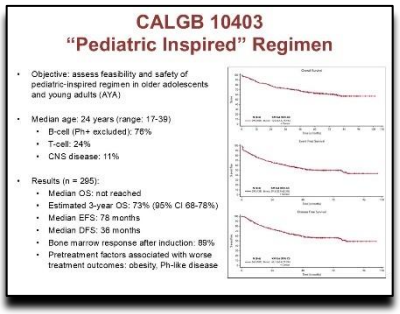
This is sort of chemotherapy-based regimen, the BFM, which is sort of the classic chemotherapy regimen used in acute lymphoblastic leukemia. In comparing this to hyper-CVAD, you see that there are sort of some differences, it looks like, in overall survival based on initial white blood cell count, which we would expect, as this is a poor prognosis feature. But that overall survival by either protocol or complete remission rates by either protocol were essentially the same, that there wasn't a lot of difference between a hyper-CVAD-based regimen and a BFM regimen.



Slide 43: ABFM Therapy in AYAs With ALL

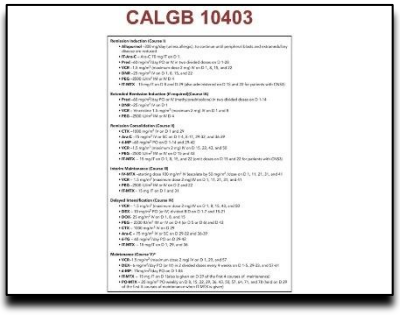
And, and the ABFM regimen is tolerable in young adult patients, but really not associated with significant improvements in overall survival or CR rates. And the shift to pediatric-based regimen for the young adults, we're still sort of evaluating; but it certainly looks like asparaginase (Rylaze®)-intensified regimens improve overall survival in young adults who have ALL. But there's a lot of toxicity, and there needs to be more study really looking at the risk-benefit ratio.

The toxicity profiles, you know, it's much more tolerable in children than it is in young adults. So, there are differences in the way that these two regimens are tolerated by patient population, the BFM, and it's a very intensive regimen and harder for our patients to tolerate. And as I said before, the high white blood cell count at baseline does remain an independent predictor of overall survival. So, a poorer risk factor; when we pull that out looking at the two regimens, that poor risk factor does favor the more intensive chemotherapeutic regimen.



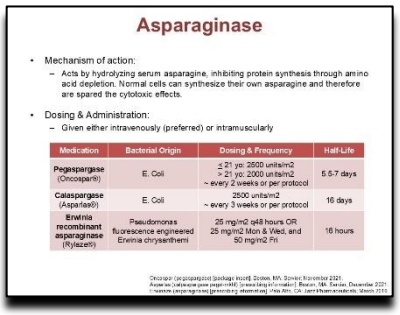
Slide 44: CALGB 10403 "Pediatric-Inspired" Regimen

CALGB 10403 was a pediatric-inspired regimen looking at the sort of feasibility and the safety of this kind of regimen in older adolescents and younger adults. The median age of patients in this trial was 24 years. The majority of patients were B-cell, and Philadelphia chromosome-positive disease was excluded in this trial. Eleven percent of patients presented with CNS disease, and, the current results available, the median overall survival has not been reached. The estimated 3-year overall survival, 73%. The median event-free survival, 78 months, and median disease-free survival, 36 months. And the bone marrow response after induction was 89%. Interestingly, the pretreatment factors associated with worse treatment outcome included obesity and Ph-positive-like disease.



Slide 45: CALGB 10403

Here is the treatment algorithm for CALGB 10403, and as you can see, it's not for the oncologist who's faint at heart. There are many drugs that are involved in this trial, and the timing is extremely important. It takes a lot of detail-oriented work on the part of the treatment and the treatment team to appropriately treat these patients. I want to also say that much of this is done outside of the hospital, so while remission induction may be done inside the hospital, the consolidation and maintenance is often done in the outpatient setting, further complicating the ability to give this regimen and requiring a real treatment team to be able to, to do this effectively in a busy outpatient practice.



Slide 46: Asparaginase

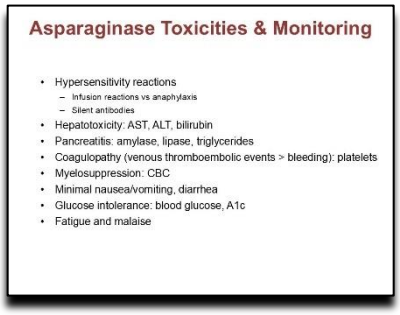
Dr. Johnson: So, asparaginase (Rylaze®) is, like we've been saying, an integral part of the backbone therapy for both pediatric and pediatric-inspired ALL patients. Asparaginase products are derived from bacteria, such as *E. coli* or *Erwinia chrysanthemi*, and they exert their activity by enzymatically depleting serum asparaginase concentrations and inhibits protein synthesis at the end of the day.

ALL leukemic cells are unable to synthesize their own asparaginase because they lack the asparagine synthetase enzyme, so they have to rely on exogenous asparaginase for survival, whereas our normal cells can synthesize their own asparagine. So, because of that, we know that asparaginase products are selectively targeting our leukemia cells. But at the end of the day, there can be some collateral damage to our normal cells because of the toxicities we're going to talk about.

It's usually preferentially given as an IV infusion for a better and more consistent absorption and, of course, less pain. But it can be given intramuscularly if needed. Asparaginase (Rylaze®) undergoes systemic degradation in terms of metabolism.

The asparaginase products listed here in this table not only differ based on their bacterial origin but also their half-life, dosing, frequency, and approved use in the different age groups.

This medication is typically given once during induction between days 4 to 15, depending on the protocol, and then throughout consolidation phases. But as we mentioned before, they don't have to necessarily be in-patient for that. The original L-asparaginase had a short half-life and was given about 3 times a week, but this hasn't been really available due to drug shortages. So, pegaspargase (Oncospar®) and calaspargase (Asparlas®) have been the two pegylated products we see most commonly used; and these both have extremely long half-lives and are given less frequently. The efficacy of these asparaginase products really depends on the drugs maintaining an adequate and prolonged depletion of asparagine, so we expect the effect of pegaspargase (Oncospar®), for example, to meet depletion for 14 days. In order to safely administer pegaspargase (Oncospar®), careful monitoring and supportive care is required to minimize or manage any clinically significant adverse effects.



Slide 47: Asparaginase Toxicities & Monitoring

It's important to keep the half-life of whichever asparaginase product you've selected for your patient in mind when you're monitoring for potential toxicities. One of the first to be aware of are hypersensitivity reactions and potential anaphylaxis. And again, this could be due to the bacterial origin of these medications and your body recognizing it as foreign.

Premedication with acetaminophen (Tylenol®) and two antihistamines typically reduce the incidence and severity of these reactions. However, there is still some debate on whether patients should truly receive these recommended premeds, because they can mask a true hypersensitivity reaction and the potential need to switch to the *Erwinia* product.

Patients should be closely monitored during and 1 hour post infusion. If a patient does experience reaction, it's important to understand the grade and severity to see if it's appropriate to resume, just at a slower infusion rate, or not rechallenge altogether. Providers may use therapeutic drug monitoring to assess asparaginase depletion and potentially detect silent neutralizing antibodies that have been deactivating enzymes and not allowing that prolonged depletion that we were talking about before. After patients receive pegaspargase (Oncospar®), the pharmacists play a huge role in ensuring appropriate labs are ordered and monitoring to detect early signs of organ damage, specifically hepatotoxicity and pancreatitis. Hepatotoxicity is usually self-resolving but occurs due to increased reactive oxygen species and mitochondrial permeability.

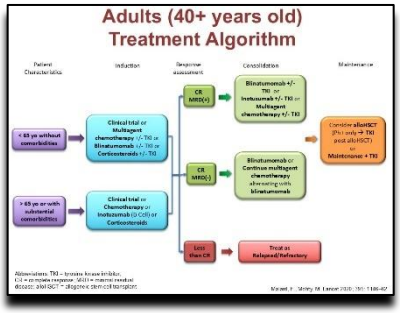
Pancreatitis has been theorized to be related to the asparagine and glutamine depletion but can also be related to elevated triglycerides, so it's just important to be monitoring these labs closely.

Pegaspargase (Oncospar®) is notoriously also known for coagulopathies but more commonly venous thromboembolic events as opposed to bleeding. And this is due to the fact that it increases tissue factor expression, induces thrombin generation, decreases antithrombin, as well as other coagulation factors.

So, you should be looking at your patients' risk factors, administer prophylactic anticoagulation with enoxaparin (Lovenox®), and counseling patients on how to identify signs or symptoms of a clot. If a clot develops, that's okay. This doesn't mean you cannot continue pegaspargase (Oncospar®). In most cases, as long as it's not severe or life-threatening, we're okay with proceeding cautiously. We just have to make sure patients are switched to therapeutic anticoagulation and monitor that clot very closely.

Other toxicities include glucose intolerance, so being mindful of patients who have diabetes at baseline, fatigue, myelosuppression as well. As you can see, there's an extensive toxicity

profile, so this is not well tolerated or, honestly, safe for adult or elderly patients, especially if you think about some of these patients already having preexisting comorbidities where we have overlapping concerns for toxicities. At the same time, this is a great role for pharmacists to really be active in the ALL patients' care. We can be reviewing baseline labs prior to each administration and make recommendations for supportive care or side effect management as needed.

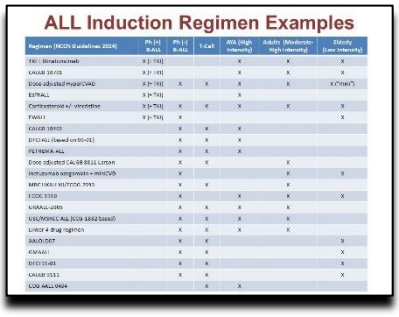


Slide 48: Adults (40+ Years Old) Treatment Algorithm

So, the treatment algorithm here, really is based on age. So patients who are 65 or younger without any comorbidities, we really think about clinical trials or multiagent chemotherapy with or without TKIs, depending on whether they're Ph-positive. And, again, when they get a CR, we think about, and they're MRD-positive, going forward with multiagent chemotherapy +/- TKI or antibody therapy with blinatumomab (Blincyto®) or inotuzumab (ozogamycin; Besponsa®) if they're MRD-positive trying to get rid of that +/- TKI, depending if they are Philadelphia chromosome-positive.

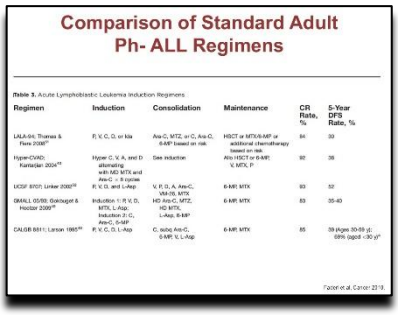
If they're CR-negative, again, potentially adding blinatumomab (Blincyto®) or continuing multiagent chemotherapy consolidation, alternating with blinatumomab (Blincyto®) or just multiagent chemotherapy on its own, depending, on the comorbidities of the patient and, again, considering allo stem cell transplant in high-risk patients.

Over 65, again, a clinical trial, chemotherapy, or inotuzumab (ozogamycin; Besponsa®) or blinatumomab (Blincyto®) with corticosteroids at the outcome which, if possible, should be done on clinical trial, again, depending on their MRD status at the end of treatment, either treating them with antibody therapy or some form of multiagent chemotherapy as consolidation or if they're MRD negative, antibody therapy or potentially some sort of multiagent chemotherapy, alternating with blinatumomab (Blincyto®). If they haven't received a CR, of course, we treat them as if they have relapse/refractory disease.



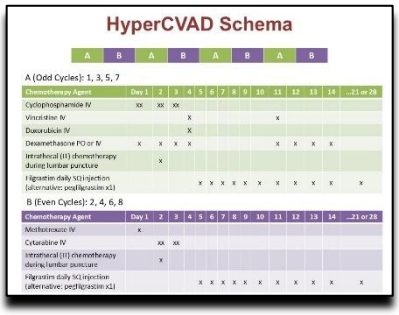
Slide 49: ALL Induction Regimen Examples

This is just a slide to show you the incredible variety of ALL induction chemotherapy regimens, none of which have really been compared in their entirety to each other. So, it's really, sort of take your pick amongst of all these and take your pick of what you're familiar with. But knowing, that certain regimens have had, very, have been very successful in particular treatment groups, like CALGB 104. So it's, a TKI plus blinatumomab (Blincyto®), may be an interesting choice in Ph-positive disease. So, it's really not a one-size fits all type of possibility.



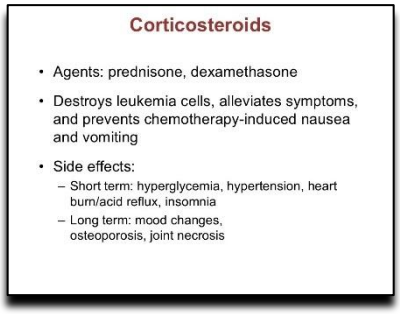
Slide 50: Comparison of Standard Adult Ph- ALL Regimens

There are some comparisons of standard adult Ph-positive ALL regimens; and, you know, looking at sort of the CR rates, of many of these regimens, they're relatively high. But where things fall apart really is at the 5-year disease-free survival rate, which can be as low as 30%, to as high as, as 50%. But the 5-year overall survival rates in patients who are older really are, are not anything near what the pediatric population experiences.



Slide 51: HyperCVAD Schema

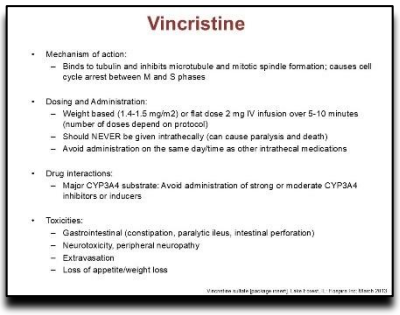
I want to sort of give you just an example of another typical treatment option for ALL, which is hyper-CVAD, which again is not an uncomplicated regimen. It's usually one that's — each cycle is given in the hospital, either partially or it's in its entirety. And there's intensive follow-up in the clinic for transfusion and to follow for infection. So, it's not an uncomplicated regimen. Even hyper-CVAD, which is amongst the easier regimens to administer in the clinic.



Slide 52: Corticosteroids

Dr. Johnson: So next we'll talk a little bit more about the induction, cytotoxic chemo, and corticosteroids a little bit more in depth. So, high-dose corticosteroids are widely used throughout all phases of ALL management, have, as we have said before, irrespective of age. And this is because it's particularly effective at destroying ALL leukemic blasts while also alleviating symptoms from extramedullary disease. As oncology pharmacists, we also know that corticosteroids have an important role in chemotherapy-induced nausea and vomiting prevention as well. So, we hit two birds with one stone when we have steroids in this management.

The most common agents are prednisone (Deltasone®) and dexamethasone (Decadron®), which are glucocorticoids. When counseling our patients, it's important to educate them on both the short-term and long-term side effects, especially if they have existing comorbidities. Oftentimes, we see acute changes in their blood glucose and blood pressure, difficulty sleeping, and changes in appetite. Pharmacists should be helping manage these side effects, such as recommending acid suppressant therapy, and optimizing hyperglycemia management. When you have to think of long-term side effects, we have to think about monitoring for mood changes, osteoporosis, and changes in appetite. But again, these are more long term and something that should be considered outpatient.

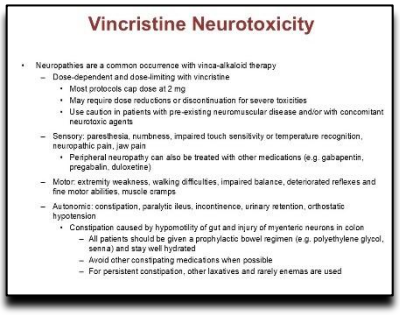


Slide 53: Vincristine

So, vincristine works by binding to tubulin and inhibits microtubule formation, causing cell cycle arrest. It should be only given intravenously, as intrathecal administration can cause paralysis and even death. ISMP best practices say we should be dispensing vincristine in a mini bag and infuse over a short period of time, and avoid giving vincristine on days patients are planned for intrathecal chemo. And this is the best ways, again, to have prevented a mix-up or any confusion.

Doses are generally capped at 2 milligrams to prevent toxicity. Vincristine is hepatically metabolized via CYP3A4, so it's important for pharmacists to review medications for drug interactions and to avoid strong CYP3A4 inhibitors or inducers when possible.
And some of the main toxicities we see are constipation, neurotoxicity, and loss of appetite. Extravasation, which is a term you see here, is when the IV catheter comes out of the blood vessel and causes leakage of the medication into the surrounding tissue. And sometimes we can see potential injury or damage.

It's important to note that the risk is generally higher in patients who already have poor veins, or they're receiving a long vincristine infusion. But this, again, extravasation is not as common in our ALL patients because we're, again giving it to them over 5 to 10 minutes, and a nurse is at bedside during administration. So, it's just something to be aware of but not likely to happen.



Slide 54: Vincristine Neurotoxicity

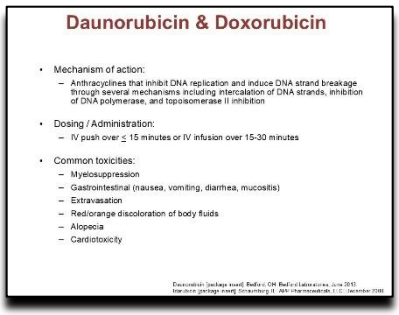
Neurological toxicities, as I touched upon earlier, are very common with the vinca alkaloids, especially vincristine; and they can manifest in either sensory, motor, or autonomic ways because they, ultimately, affect the nerves. It is dose-dependent and dose-limiting, so we oftentimes have to reduce the dose or delay doses in patients who have severe neurotoxicity manifestations that affect their daily activities.

Sensory neurotoxicities are paresthesias, numbness, impaired touch sensitivity, neuropathic pain, or jaw pain. In patients who maybe have a baseline neuropathy from, let's say, uncontrolled diabetes, pharmacists can have a role in recommending and optimizing the correct neuropathic pain management so that we don't have any interruptions in vincristine therapy.

Motor is usually rare but presents as leg weakness, difficulty walking, reduced flux, reflexes, and fine motor abilities. And then autonomic, which I think is the most common, is when patients experience constipation, urinary retention, or orthostatic hypotension. The

mechanism behind, let's say, vincristine-induced constipation is about the hypomotility of the gut and the injury of the myenteric neurons that are lining the colon specifically.

So, all patients should be receiving a prophylactic bowel regimen, staying well-hydrated, and avoiding other constipating medications when possible. And this will help us avoid patients getting into more of a paralytic ileus state. For patients with persistent constipations: again, pharmacists can recommend other laxative therapies to optimize, but we really should be avoiding enemas in our patients, especially those are neutropenic.

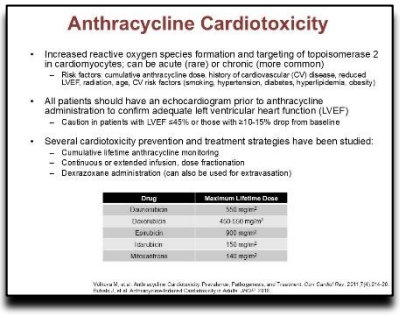


Slide 55: Daunorubicin & Doxorubicin

Anthracyclines are going to be the last important backbone of our intense ALL induction and consolidation therapy management, and the two most commonly used in ALL are daunorubicin (Cerubidine®) and doxorubicin (Adriamycin®). Anthracyclines work by inhibiting DNA replication and inducing DNA strand breakthrough due to different mechanisms, including intercalation of the DNA strands and inhibition of DNA polymerase and topoisomerase II. Like I had mentioned earlier on a presentation, we usually give this to patients who are fit and generally less than the age of 60, because they need to have an adequate ejection fraction. They're both given intravenously through a short 15- to 30-minute push or infusion, and they undergo hepatic metabolism. So, something to just keep in mind when you have patients with underlying liver dysfunction.

In terms of toxicity, myelosuppression is by far the main one to expect. So, they can see, patients can see worsening in their blood counts before they see eventual normalization. Patients tend to have moderate nausea and vomiting, so they'll receive 2 premedications prior to administration. And extravasation is technically possible since it is also a vesicant, but it's quite rare because it's infused over a short period of time, just like vincristine.

One of the other notable toxicities with these anthracyclines is that patients may notice their bodily fluids — such as urine, sweat, or tears — temporarily turn a little bit orange or red tinge in color. And it's important to just counsel your patients to let them known this is completely normal and should not cause any panic. This is ultimately because the chemotherapy itself is red, and your body is just eliminating it. And then the final and most arguably and most important toxicity related to anthracyclines is its effect on the heart or cardiotoxicity.



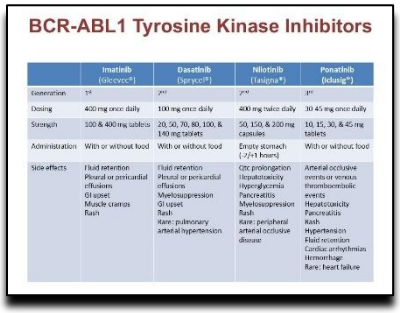
Slide 56: Anthracycline Cardiotoxicity

So the mechanism of anthracycline-induced cardiotoxicity is multifactorial, but it essentially boils down to the fact that it causes direct injury to the cardiomyocytes, and there's increased oxidative stress over time on these cells. Cardiotoxicity can manifest in one of two ways. Acute cardiotoxicity, which is secondary to more of an inflammatory response, can present as palpitations or arrhythmias. But this is very rare. Whereas chronic cardiotoxicity is more commonly seen in our patients, and this is when patients experience a decrease in ejection fraction over time, and we see cardiomyopathy, decrease in ejection fraction related to heart failure, etc.

So prior to initiating anthracyclines, patients need a baseline echocardiogram to confirm what their ejection fraction is; and this will tell us how well their heart is pumping. We'll also assess any risk factors that might increase their risk of chronic cardiotoxicities, so this includes heart disease, age, radiation exposure, smoking, high blood pressure, etc.

So, if your patient has an ejection fraction below 45 or 50%, or there's a significant drop from their baseline, these patients are most likely not a candidate for anthracycline therapy. So, one of the main risk factors that I didn't mention yet, but I want to touch upon a little bit more, is previous exposure to anthracyclines, which we track as pharmacists with each treatment. The table below lists the cumulative anthracycline dose patients are allowed to have in their lifetime, because the closer you are to this number, the higher the incidence of cardiomyopathy. This is particularly important for a patient who's been treated with anthracyclines with a past medical history of breast cancer, for example, who may have received 4 cycles of AC (anthracycline); and they got 240 milligrams per meter squared of doxorubicin (Adriamycin®) already. If their ejection fraction is still okay, we can still proceed with an anthracycline-based regimen, but we have to take into account how much anthracycline they're allowed to have left to avoid that toxicity.

There are a few strategies to prevent and monitor cardiotoxicity. Even though these strategies aren't commonly used, they're worth knowing, so I'll just briefly touch upon them. Besides the ejection fraction assessments and lifetime dose tracking, we can technically extend the duration of the infusion or fractioning the doses over several days to get less of a peak effect. There's some data with ACE inhibitors or ARBs to have a cardioprotective effect. And then last but not least, the dexrazoxane (Zinecard®), which is typically used as a, for extravasation. It can also be used as a cardioprotectant in patients who may have already received a certain amount of anthracyclines.



Slide 57: BCR-ABL1 TKIs

So then, for our 25% of patients who have Ph-positive B-ALL and select patients with Ph-like B-ALL, they will receive an oral tyrosine kinase inhibitor or TKI in addition to their cytotoxic chemotherapy and/or steroids. And really what these drugs do is that it targets the overactive tyrosine kinase that's normally promoting uncontrollable cell growth and division, and this protein is being produced by the BCR-ABL fusion gene.

We know that it significantly improves outcomes; and it's truly changed the prognostic significance of having a Philadelphia chromosome. So, it's important that as a pharmacist, one of these drugs is added to your patient's regimen no matter what.
As you can see from this chart, there's several approved BCR-ABL TKIs in the ALL setting. So, it's our shared responsibility as pharmacists to assist in selecting the best agent for our patient, alongside with our oncologist colleague.

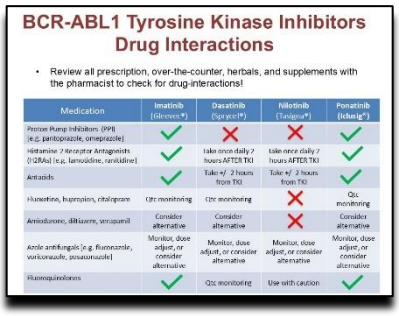
There are three generations of BCR-ABL TKIs, and you may recognize some of these agents actually overlapping the CML, or chronic myeloid leukemia, space as well. But ultimately, our TKI choice should be individualized and depends on patient and treatment-specific factors, such as their dosing frequency, the administration, side effects, et cetera. And we have to also pick it based off of their side effect profiles.

The first BCR-ABL approved was imatinib (Gleevec®), but this has largely fallen out of favor for up-front ALL therapy because we've had other TKIs introduced over the last couple years that we preferentially use. So, one of these drugs would be ponatinib (Iclusig®), which is a third-generation TKI; and it's preferred up front for our newly diagnosed Ph-positive B-ALL patients in combination with chemo.

If ponatinib (Iclusig®) is not available or appropriate for a patient, a second-generation TKI such as dasatinib (Sprycel®) may be used instead. It's important that we also account for drug interactions, ease of administration, overlapping toxicities, or warnings with existing comorbidities, and then ultimately, their response to treatments. So, if you select dasatinib (Sprycel®), for example, up front, and we see that their BCR-ABL PCR has not improved over the milestones that we're looking for, we oftentimes see providers switching the TKI choice.

So, just to give an example here, you can see like nilotinib (Tasigna®), for example, is the only agent here that requires patients to be on an empty stomach; and, while they're taking their medication twice a day, so in a patient who you're maybe concerned about noncompliance, nilotinib (Tasigna®) may not be the best choice.

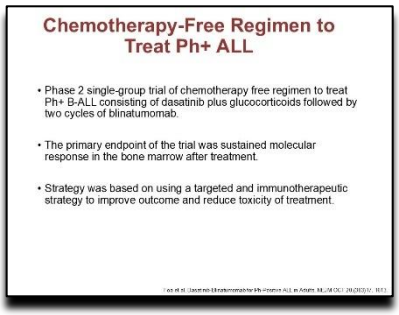
For patients with a history of pleural effusions or pulmonary hypertension, dasatinib (Sprycel®) might not be the best choice. In patients with an extensive cardiopulmonary history with clots or several heart attacks, arrhythmias, ponatinib (Iclusig®) or nilotinib (Tasigna®) may also not be the best choice. But we have to weigh the risk versus benefits and see what we can do from there.



Slide 58: BCR-ABL1 TKIs: Drug Interactions

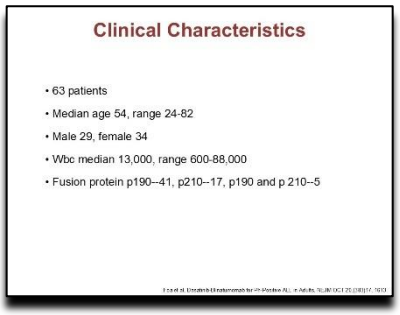
Before initiating the TKI, the pharmacist should be interviewing your patients and reviewing for the drug interactions, whether it's prescription, over the counter, herbals, or supplements. This will ensure we do our due diligence adjusting the dose or modifying therapy while avoiding either too high or too low levels of these TKIs. So, one of the most common medication and drug interactions we encounter are acid suppressant therapies. So, if your patient is on or needs to start a PPI, they cannot be on dasatinib (Sprycel®), or nilotinib (Tasigna®). We can make one of two modifications, depending on what's more appropriate. Patients should switch to an H2RA or an antacid and space them out appropriately if they want to remain on dasatinib (Sprycel®) or nilotinib (Tasigna®). Whereas if a PPI cannot be avoided, let's say in an active GI bleed, then the TKI needs to be switched to ponatinib (Iclusig®) or imatinib (Gleevec®). Otherwise, their efficacy will be greatly reduced.

Nilotinib (Tasigna®) is known for QTc prolongation, more than the other TKIs. So, avoiding or using caution with certain antidepressants or cardiac medications are critical. For the for the other TKIs, QTc monitoring is typically sufficient. For CYP3A4 inhibitors like azole antifungals, you can either monitor on the full doses, dose-adjusted TKI, or consider an alternative agent to avoid this interaction.



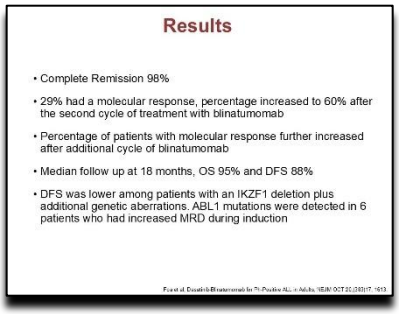
Slide 59: Chemotherapy-Free Regimen to Treat Ph+ ALL

Dr. Ritchie: So, recently, there have evolved chemotherapy-free regimens to treat ALL, particularly Ph-positive ALL as an up-front regimen for patients with this disease. This was a relatively exciting Phase II trial that was published in the *New England Journal of Medicine* using dasatinib (Sprycel®) and gludicocorticoids followed by 2 cycles of blinatumomab (Blincyto®). And the primary endpoint of this trial was sustained molecular response in the bone marrow after treatment; and the strategy was based on using sort of targeted and immunotherapeutic strategy to improve outcome and reduce the toxicity of treatment.



Slide 60: Clinical Characteristics

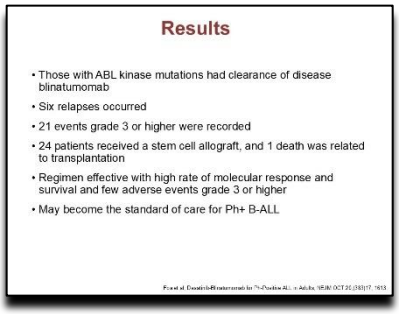
This was a relatively small study — 63 patients with a median age of 54. Males and females well-balanced, and the fusion proteins included P190, P210-17, and P210-5.



Slide 61: Results

The results were, were striking. There was a complete remission rate in 98% of patients; 29% had a molecular response, and the percentage increased to 60% after the second cycle of treatment with blinatumomab (Blincyto®). The percentage of patients with molecular response further increased after an additional cycle of blinatumomab (Blincyto®). And at the median follow-up of 18 months, overall survival was 95%, and disease-free survival was 88%.

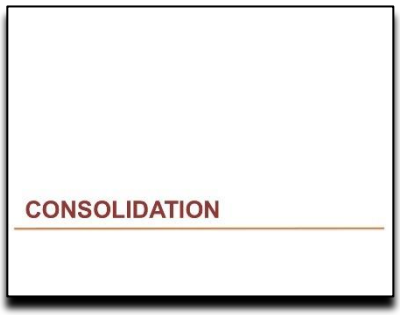
The only caveat here was disease-free survival was lower among patients with an IKAROS deletion plus additional genetic aberrations, and ABL mutations were detected in 6 patients who had increased MRD during the induction cycle.



Slide 62: Results

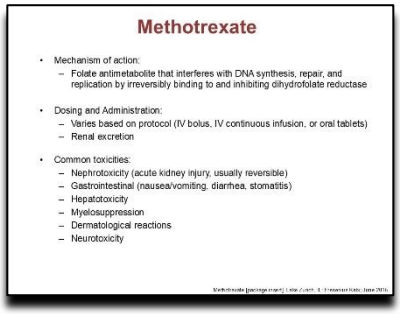
Those with ABL kinase mutations did have clearance of disease with blinatumomab (Blincyto®). There were 6 relapses which occurred. There were 21 events that were Grade 3 or higher that were recorded on this trial, but that's expected really in an ALL induction trial.

Twenty-four patients did receive a stem cell allograft. One death was related to transplantation. The regimen was very effective, with a high rate of molecular response and survival and few adverse events of Grade 3 or higher. And this is probably going to become a standard of care for the patients that present with Ph-positive ALL, which is very exciting. It's a chemo-free regimen and potentially much of it given outside of the hospital.



Slide 63: Consolidation

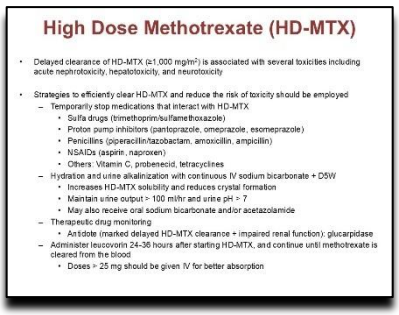
After induction therapy, we move onto consolidation therapy, which is what we use to try and keep patients in remission after they have had their initial chemotherapy. And the agents used are going to be discussed by Cathy.



Slide 64: Methotrexate

Dr. Johnson: So the first agent we'll talk about is high-dose methotrexate; and methotrexate is a very common agent used not only in ALL consolidation, but you might also see it being used in other disease states as well. But for our purposes, IV high-dose methotrexate is necessary for ALL consolidation. It works by binding to dihydrofolate reductase, and this inhibits the reduction of folates and thymidylate synthetase. Methotrexate is metabolized in various pathways but primarily through hepatic oxidation and intracellular glutamation. It is renally excreted, so we have to be thoughtful about how to safely administer high-dose methotrexate in patients who are at risk for accumulation. So, older patients, patients with baseline renal impairment, or third spacing.

There is a wide range of toxicities, but it is somewhat dose dependent. The mean is myelosuppression. The degree of nausea, vomiting, and diarrhea, and even stomatitis or like mucositis increases with the dose. You can also see liver function lab abnormalities but usually at higher doses. Nephrotoxicity and neurotoxicity are rare, but in the instance that does happen, it occurs with high-dose methotrexate.



Slide 65: High Dose Methotrexate (HD-MTX)

So, when I say high-dose methotrexate, I'm specifically referring to intravenous doses greater than or equal to 1,000 milligrams per meter squared, as this is the dose needed to penetrate the blood-brain barrier. Exposure to high-dose methotrexate concentrations for a short period of time is associated with nephrotoxicity, hepatotoxicity, and neurotoxicity. For patients with delayed clearance of their high-dose methotrexate, they can experience an acute tubular necrosis type of picture; and this is because the methotrexate is crystallizing in these tubules.

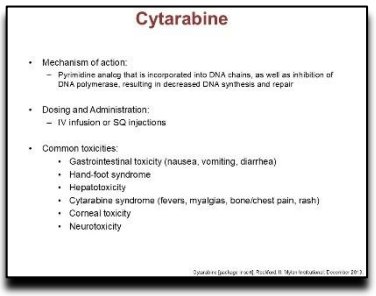
We can see an increase in serum creatinine, but usually urine output is maintained. Exposure to low concentrations for a long period of time is when we're going to see more prolonged myelosuppression; gastrointestinal toxicities, such as mucositis.

So, when we plan on administering high-dose methotrexate in the hospital, there are several strategies as pharmacists we need to make sure are employed to ensure high-dose methotrexate is efficiently cleared and prevent these toxicities from happening to our patients. So, first before starting, it's important that we carefully review and temporarily hold any medications that may impair clearance, inhibit active tubular transport, acidifies the urine, or displaces methotrexate from protein binding sites.

These medications include sulfa drugs, proton pump inhibitors, penicillins, NSAIDs, and vitamin C. If these medications are necessary to be given during high-dose methotrexate, we can always find an alternative that's appropriate. So, for example, dapsone (Avosulfon®) instead of Bactrim™ (sulfamethoxazole and trimethoprim), famotidine (Pepcid®) instead of pantoprazole (Protonix®), cefepime (Maxipime®) instead of Zosyn® (piperacillin and tazobactam), et cetera.

Patients are also started on high rates of IV sodium bicarbonate, typically 150 mEqs and D5W. And this ensures vigorous hydration and urine alkalinization. Our goal is to maintain a urine output greater than 100 cc's per hour and a urine pH greater than 7. Alkalinized urine increases methotrexate solubility and reduces crystal formations, so this will help expedite the clearance process. Once this is done, we can initiate high-dose methotrexate. And, depending on the protocols, either infused over 24 hours or between 3 to 6 hours.

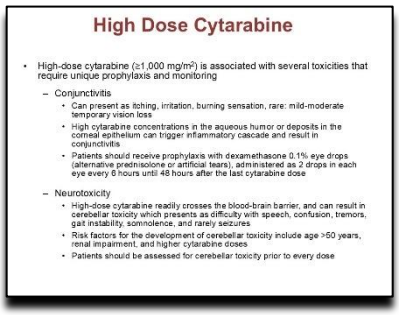
Therapeutic drug monitoring of our serum methotrexate levels at the 24-hour intervals are crucial because we are evaluating the clearance against set goals we have using a nomogram. Leucovorin, which is a derivative of tetrahydrofolate, must be administered 12 to 24 hours after high-dose methotrexate is complete. And this allows maximum cytotoxic activity before we rescue and protect those healthy cells. One of the common misconceptions that we as pharmacists can help educate on is that leucovorin does not help clear methotrexate, but, rather, it's just protecting your healthy cells. Any dose greater than 25 milligrams of leucovorin should be given IV for adequate absorption. In patients with significantly delayed methotrexate clearance and marked acute kidney injury, we may need, on occasion, to consider the antidote glucarpidase (Voraxaze®), but this is not commonly needed for our ALL patients. But it's good to know just in case you encounter this issue.



Slide 66: Cytarabine

The other common agent used in ALL consolidation is cytarabine (Cytosar®), which is a pyrimidine analog that gets incorporated into DNA chains and inhibits DNA polymerase, ultimately decreasing DNA synthesis and repair. Although there seems to be a wide range of toxicities for cytarabine (Cytosar®) as well, just like methotrexate, it is a dose-dependent effect; and it impacts the type and likelihood of what you'll experience. So, we can see nausea, vomiting, and diarrhea at any dose; but, obviously, the higher the dose, the higher the chances. This is why preventative antiemetics

are important as well. Some patients experience rash, low-grade fevers, or itchings of their sole in their feet. And then, last but not least, corneal and neuro-toxicity are rare and tend to only occur at high doses.

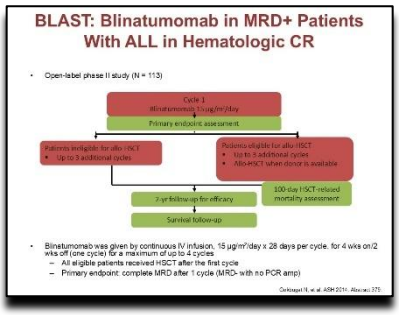


Slide 67: High-Dose Cytarabine

High-dose cytarabine (Cytosar®) is also defined as greater than or equal to 1,000 milligrams per meter squared. When we administer high-dose cytarabine (Cytosar®), there are also unique preventative measures and monitoring we need to do when they're in the hospital. Chemical conjunctivitis or corneal toxicity occurs because the high-dose cytarabine (Cytosar®) concentrations are in the aqueous humor and deposits in the corneal epithelium as well. And this triggers an inflammatory response. So, some patients can experience itching, burning sensations, irritation, and in rare cases have pain or a temporary vision loss.

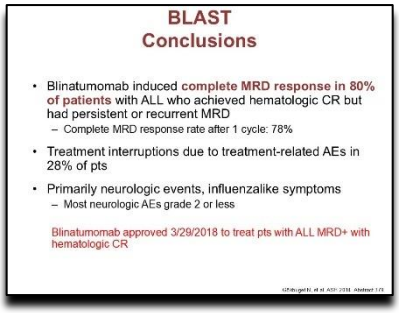
This toxicity is rarely seen due to two reasons. In patients who are older or have poor kidney function, we reduce the dose and, subsequently, the risk of this side effect from happening. And two, all our patients are required to receive preventative eye drops throughout and after treatment. So, typically, patients receive 2 doses of dexamethasone (Decadron®) eye drops in each eye every 6 hours on the day that they receive cytarabine (Cytosar®) and for 2 to 3 days after the last cytarabine (Cytosar®) dose. The frequent eye drops help to flush the eye, and the steroid component helps decrease any associated inflammation. And in the event of a drug shortage, prednisolone eye drops or artificial tears are acceptable alternatives.

The other key toxicity you see here is neurotoxicity, which happens because this drug is crossing the blood-brain barrier. Neurotoxicity can be presenting in patients as difficulty with speech, or gait, confusion, tremors, somnolence, and, in rare scenarios, seizures. So, patients who are at high risk tend to be the patients above the age of 50. They have baseline kidney dysfunction, and they're also receiving high doses. So, maybe for our older patients, we will reduce the dose of cytarabine (Cytosar®) to avoid this from happening. And our nurses do a good job of having our patients write their name prior each dose and tracking any subtle changes in their hand movement or signature, because even the smallest sign can indicate cerebellar toxicity. If any of these toxicities were to occur, we would immediately stop cytarabine (Cytosar®).



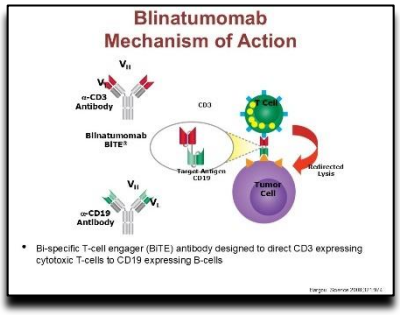
Slide 68: BLAST: Blinatumomab in MRD+ Patients With ALL in Hematologic CR

Dr. Ritchie: So, there are alternatives to chemotherapy treatment and consolidation therapy for patients with ALL. And one of the most promising for all of us has been the use of blinatumomab (Blincyto®). The BLAST study looks at blinatumomab (Blincyto®) in MRD-positive patients with ALL who have a hematologic CR. So the marrow looks fine, but we notice that the patient is MRD-positive. And this was an open-label, Phase II study of 113 patients where they got a cycle of blinatumomab (Blincyto®); patients who were ineligible for allo stem cell transplant got up to 3 additional cycles, and patients who were eligible for allogeneic stem cell transplant got up to 3 additional cycles and went to allo transplant when a donor was available. The endpoint was looking for a 2-year follow-up for efficacy and for survival.



Slide 69: BLAST Conclusions

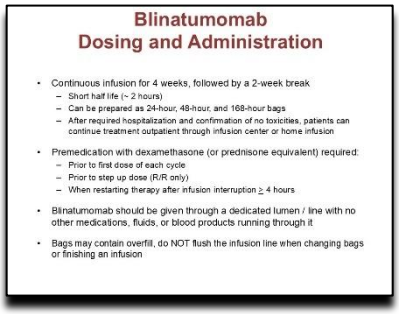
The findings in this trial were that blinatumomab (Blincyto®) induced a complete MRD response in 80% of patients with ALL who achieved hematologic CR but had persistent or recurrent MRD. And the complete MRD response after cycle 1 was 78%. Treatment interruptions due to AEs were, occurred in 28% of patients. Those were primarily neurologic events or influenza-like syndrome, and most neurologic AEs were Grade 2 or less; and this led to the approval of blinatumomab (Blincyto®) in 2018 to treat this group of patients who were MRD-positive with hematologic CR.



Slide 70: Blinatumomab: Mechanism of Action

So, how does blinatumomab (Blincyto®) work? Well, it's a bispecific T-cell engager or BiTE, monoclonal antibody therapy that binds to and targets CD19 on our B cells and CD3 on our T cells. And this ultimately causes the production of cytolytic proteins, the release of inflammatory cytokines, CT cell proliferation, and ultimately cytotoxicity of these leukemic cells.

So, it's a very exciting immunotherapy option for our patients. It is approved for CD19-positive B-cell ALL patients with relapsed and/or refractory disease, as well as patients for consolidation with or without minimal residual disease.



Slide 71: Blinatumomab: Dosing and Administration

So, the initial dose for blinatumomab (Blincyto®) depends on the indication. But the maximum dose is 28 micrograms for patients over 45 kilograms. One of the most unique aspects of blinatumomab (Blincyto®) that needs to be emphasized to patients before starting is that this is given as a continuous infusion over 4 weeks, followed by a 2-week break. And this is due to the short half-life of the medication. They are investigating a subcutaneous formulation, but until then, patients need to understand how this will impact their day-to-day life, as they will be connected to some form of an IV bag upon discharge when they complete the necessary hospitalization days for toxicity monitoring.

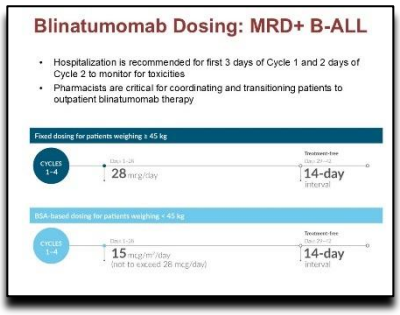
Blinatumomab (Blincyto®) bags can be prepared to last 1, 2, or 7 days; and the 7-day one has preservatives. The longer durations tend to be used more so in the outpatient setting. Before receiving blinatumomab (Blincyto®), before escalating any dose, and in the event that we have to stop the infusion for 4 or more hours, patients need to receive dexamethasone (Decadron®) 60 minutes prior.

It has like a minimal emetogenic potential. It lacks clinically significant drug interactions and has no renal or hepatic dose adjustments, so, generally, it's well tolerated and easier to manage from that perspective. But there are some toxicity and logistical considerations that we have be mindful of. And as pharmacists, we can help educate both our colleagues and patients on. So, blinatumomab (Blincyto®) should be given through a dedicated lumen or line. It can be given peripherally, but for easy, uninterrupted patient access, even outpatient, central venous catheters are important.

It is also critical that no other medications, fluids, or blood products are running through it or labs are being drawn from that lumen; and this is because we want the blinatumomab (Blincyto®) concentrations in the blood to remain constant and that there's no fluctuations in the body levels.

The bag usually contains overfill, and this is to account for the fact that the IV line is primed and that the bag does not run out before 24 hours, again, because we want to minimize any unnecessary interruptions. So, if there are any remainders of the 24-hour mark, that's fine. The bags still need to be exchanged at the 24-hour mark.

It's important not to flush the infusing line, especially when you're changing the bags because, again, the line is primed. Patients will receive a rush of bl-, blinatumomab (Blincyto®) at once, and they can experience toxicities.

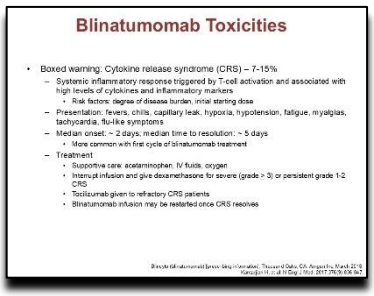


Slide 72: Blinatumomab Dosing: MRD+ B-ALL

In patients receiving blinatumomab (Blincyto®) for consolidation therapy, whether they're MRD-positive or negative, they will be started at the full 28 microgram dose — if they weigh more than 45 kilos — and 15 mcg per meter squared per day if less than 45 kilos.

These patients don't require a dose escalation because they have little to no disease burden, so their risk of toxicities is less. And patients are given up to four 42-day cycles of blinatumomab (Blincyto®) consolidation.

When blinatumomab (Blincyto®) is given in this setting, patients are admitted for the first 3 days for cycle 1 and first 2 days of cycle 2. And once patients have proven tolerance, they can be discharged the following day on an outpatient CADD pump and continue treatment either through the infusion center — and so they come back to clinic —, or they can continue through home infusion if that is an available option for them. Pharmacists are crucial in helping our physician and nursing colleagues with education and coordination to make sure that there's ultimately a smooth transition for outpatient blinatumomab (Blincyto®) treatment. And once they've proved tolerance, they can continue subsequent cycles outpatient.



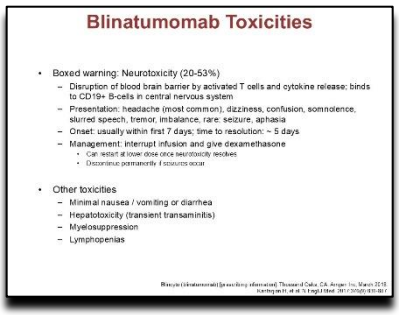
Slide 73: Blinatumomab Toxicities

There are two black boxed warnings associated with blinatumomab (Blincyto®) that warrants the hospitalization and close monitoring that we've been emphasizing since the beginning. The first is cytokine release syndrome, or CRS, and this is a systemic inflammatory response triggered by T cell activation; and it's associated with those elevated cytokines and inflammatory markers.

Patients can experience 1 or more of the following flu-like symptoms, so fever, chills, low blood pressure, low oxygenation, fast heart rate, as well as like fatigue. CRS's were more commonly seen in the first cycle of blinatumomab (Blincyto®) treatment, and this makes sense because when you're thinking about a disease burden, it's oftentimes greater if at all in the first cycle. But again, it's not always dependent on the degree of disease burden, because it can happen even in patients with minimal residual disease negativity.
It usually occurs within the first 2 days, and the median time to resolution for high-grade CRS is usually 5 days; but in clinical practice, especially for low grade, it resolves within 24 hours.

We want to provide the correct supportive care based on their symptoms, so whether that's acetaminophen (Tylenol®) for fevers, fluids for low blood pressure, oxygen for low oxygen status, those are things that need to be done promptly, and we can do this without holding

the infusion. But if, despite the supportive care we're giving, the CRS is severe or persistent, then we may need to hold the infusion and give dexamethasone (Decadron®) immediately. In cases where dexamethasone (Decadron®) is still not proven to be effective, then we're going to add tocilizumab (Tyenne®) as well. And we can restart the blinatumomab (Blincyto®) in most cases as long as it's not severe CRS. But sometimes our providers would like to start at a lower dose first. If the CRS is life-threatening or your patients require mechanical ventilation, then it would be appropriate to discontinue blinatumomab (Blincyto®) altogether.

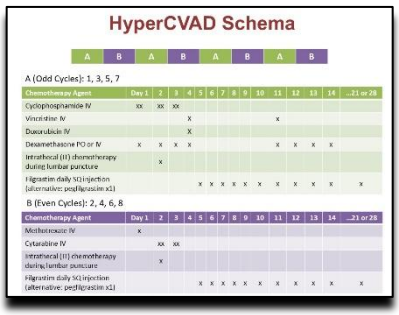


Slide 74: Blinatumomab Toxicities

The second most important toxicity is neurotoxicity, which results from these activated T cells and cytokines crossing and disrupting the blood-brain barrier; and there could potentially be some CD19-positive B cells in the CNS space as well that blinatumomab (Blincyto®) is targeting. Patients with a history of, or current CNS disease, were excluded from the clinical trial, so it's kind of hard to say how this would impact or increase the risk. But if your patients are experiencing headaches, which tends to be the most common, dizziness, confusion, somnolence, slurred speech and tremors, this could be a sign of neurotoxicity.

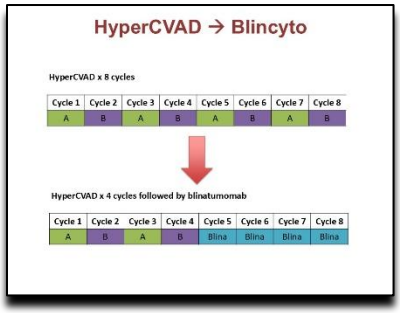
In very rare situations, and clinical trials have noted this to happen, seizures could be a possible manifestation of neurotoxicity. And if this were to happen, we would stop blinatumomab (Blincyto®) altogether, start steroids, and antiepileptic therapy to make sure that we're managing the seizures.

If it's a less severe manifestation, like with the headaches and things that we talked about, we should be temporarily holding the infusion, give steroids and other supportive care, but we can rechallenge these patients, just at a lower dose. If they're outpatient, it's important that we counsel patients even after they get discharged and they didn't have neurotoxicity with the first couple of days. They should be cautious of this, maybe potential delayed neurotoxicity; so driving, operating heavy dangerous machinery — those are all things that they should be a little bit more thoughtful about avoiding. Other toxicities to be aware of: again, diarrhea, some transient transaminitis, and mild myelosuppression, but overall, otherwise well tolerated by our patients.



Slide 75: HyperCVAD Schema

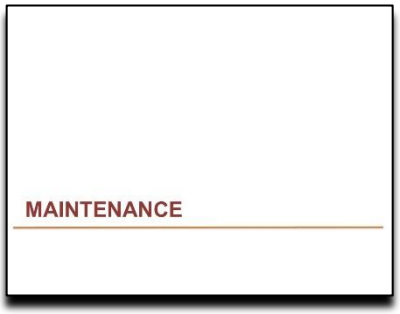
Dr. Ritchie: Now, we show again the hyper-CVAD schema, which is multiagent chemotherapy; and you can see that, Cytoxan® (cyclophosphamide) that we talked about earlier and methotrexate are incorporated into the cycles A and B of hyper-CVAD in order to facilitate consolidation. But it's also now thought that it's a good schema to introduce Blincyto® (blinatumomab) into.



Slide 76: HCVAD → Blinatumomab

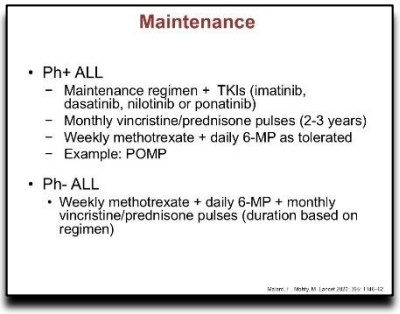
Where, in addition to giving the general cycles A and B of hyper-CVAD, that we incorporate blinatumomab (Blincyto®) into their consolidation cycles so that the first 4 cycles of treatment follow the traditional hyper-CVAD alternating cycle A with Cytoxan® (cyclophosphamide) with cycle B with methotrexate. But in cycle 5, that we began 4 cycles of blinatumomab (Blincyto®) to actually improve the outcome in patients who are receiving consolidation therapy with hyper-CVAD.

So, it's sort of a new way of looking at consolidation therapy to incorporate Blincyto® (blinatumomab) into this algorithm with the hope of improving the duration of response and overall survival.



Slide 77: Maintenance

We'll now talk a little bit about maintenance chemotherapy.

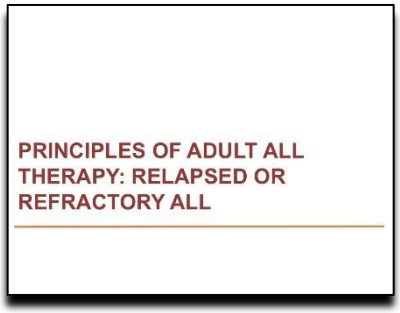


Slide 78: Maintenance: NCCN Guidelines

Maintenance chemotherapy is sort of the final phase of chemotherapy after intensive chemotherapy has been completed to treat patients with ALL. Maintenance chemotherapy in patients who are Ph-positive really are TKIs. For patients who can tolerate additional therapy to TKIs, monthly vincristine and prednisone (Deltasone®) for 2 to 3 years, depending upon the protocol used, and weekly oral methotrexate as tolerated. So, it's the so-called POMP maintenance together with TKIs. Many patients with Ph-positive ALL cannot tolerate all of

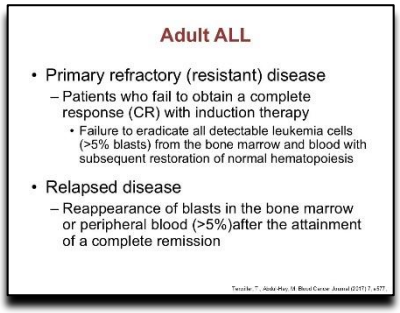
these agents at one time, but we certainly make an effort to continue TKIs ongoing in these patients.

For Ph-negative ALL, we follow a traditional POMP maintenance schedule, depending upon the protocol whether we do 2 to 3 years of weekly methotrexate, daily 6-MP, and monthly vincristine and prednisone (Deltasone®).



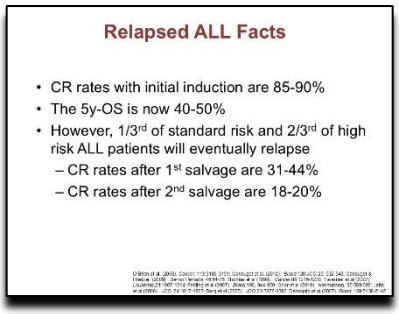
Slide 79: Principles Of Adult All Therapy: Relapsed Or Refractory ALL

What do we do about patients with relapsed or refractory disease? What are our options?



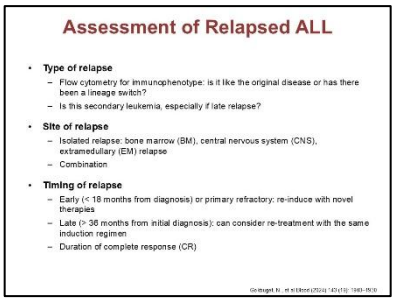
Slide 80: Adult ALL

Adult ALL with primary refractory or resistant disease, we define those as those patients who failed to obtain a complete response with induction chemotherapy. So, the failure to eradicate detectable leukemia cells, greater than 5% blasts from the bone marrow and blood, with subsequent restoration of normal hematopoiesis. Relapsed disease we defined as a reappearance of blasts in the bone marrow or peripheral blood of 5% or greater after an attainment of complete remission.



Slide 81: Relapsed ALL Facts

Relapsed ALL, sort of the facts are the CR rates with initial induction are really about 85 to 90%. But the 5-year overall survival is 40 to 50%. One-third of standard risk and two-thirds of high-risk ALL patients eventually relapse, and the CR rates after first salvage are, are low — 31 to 44% of patients. And after second salvage, even lower, 18 to 20% of patients.

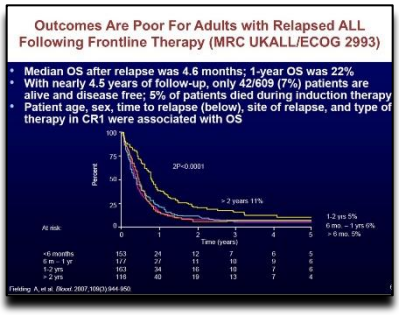


Slide 82: Assessment of Relapsed ALL

How do we assess relapsed ALL? We assess again by immunophenotype. Is it like it's original disease, or has there been a lineage switch, which can happen? Very important to reassess the disease at the time of relapse. Is it a secondary leukemia after treatment of the first? Is it now an AML that is treatment related, for example, or is it the same disease that he or she had initially?

It's important to determine the site of relapse. Is it in the bone marrow? Is it a primary CNS relapse? Is it extramedullary disease? Is it a combination of all of them? It's important to assess whether, again, the CNS to make sure it's not involved at the time of relapse and to look for extramedullary disease.

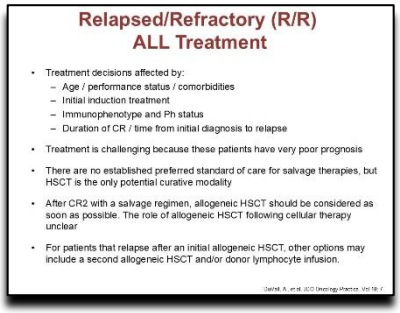
The timing of relapse is really important in determining the treatment of the disease. Is it early? Less than 18 months from diagnosis, or is it primary refractory where they did not attain a complete remission with MRD-negativity after 4 weeks of treatment? Is it late, 36 months or greater after the initial diagnosis and treatment? And what was the duration of the response? Was it a couple of months or was it years?



Slide 83: Outcomes Are Poor For Adults with Relapsed ALL Following Frontline Therapy (MRC UKALL/ECOG 2993)

The outcomes are poor for adults with relapsed ALL following frontline therapy. This is data from the MRC/ECOG 2993. The median survival after relapse is 4.6 months, and the overall survival at 1 year, 22%. And at nearly 4.5 years of follow-up here, only 7% of patients were alive and disease free, and 5 percent of patients died during induction therapy.

Patient age, sex, time to relapse, site of relapse, and type of therapy in CR1 were associated with overall survival.

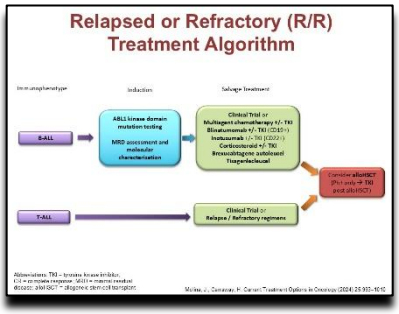


Slide 84: Relapsed/Refractory (R/R) ALL Treatment

Treatment decisions are affected by age, performance status, and comorbidities just as they are at initial treatment. And this may have changed since the original induction for this particular patient. We look at the initial induction treatment, and we think of potentially doing something different if the remission has been of a short period of time. We look at the immunophenotype again and Philadelphia chromosome status, and we look carefully at the duration of the CR. How

long did that initial CR last? Treatment is very challenging, because these patients have a poor prognosis. There is no standard of care or salvage therapy, but the only curative modality at this point in time is a stem cell transplant.

After the second CR with the salvage regimen, stem cell transplant should be considered as soon as possible. And the role — if we have used cellular therapy like a CAR-T — the role of allogeneic stem cell transplant is not completely clear. For patients that relapse after initial allogeneic stem cell transplant, other options may include a second transplant or donor lymphocyte infusion, if appropriate.

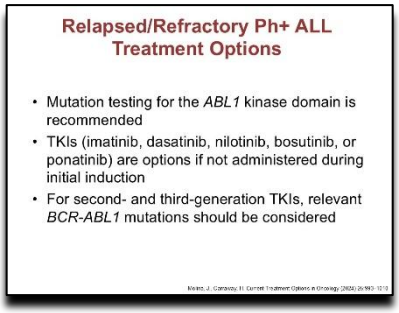


Slide 85: Relapsed or Refractory R/R Treatment Algorithm

So the treatment algorithm for relapsed/refractory disease for B-ALL, again, we want to see whether there is ABL kinase domain mutations; and we look at MRD and these characterization in these patients to see whether or not they've responded to salvage chemotherapy.

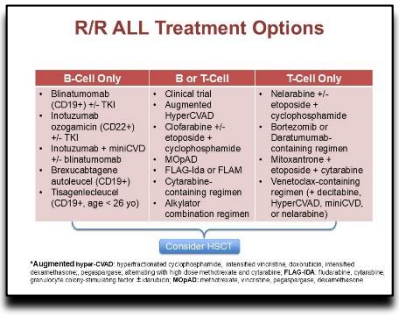
Our salvage therapies, you know, include multiagent chemotherapy +/- TKIs, depending on, on Philadelphia chromosome status. A blinatumomab (Blincyto®), inotuzumab (ozogamycin; Besponsa®), or brexucabtagene autoleucel (Tecartus®) or tisagenlecleucel (Kymriah®) has possibilities for salvage treatment. Again, we consider allogeneic stem cell transplant if a donor is available and it's appropriate.

For T-ALL, we have fewer choices. It's best if we can enroll these patients on a clinical trial. Again, what's left for us is really multiagent chemotherapy regimens with a plan for allo transplant.



Slide 86: Relapsed/Refractory Ph+ ALL Treatment Options

For relapsed/refractory Ph-positive ALL, the treatment options are great. The mutation testing for ABL kinase domain is recommended. Choosing a TKI, usually the TKI which was not used initially will work; but looking at ABL kinase domain, mutation testing which TKIs may be more appropriate for your patient. Second- and third-generation, TKIs should be considered for these patients. Dasanitinib (Sprycel®), it's a possibility for these patients. There is clinical trials open for new and novel TKIs. These are all possibilities in patients who are Ph-positive for relapse after treatment.

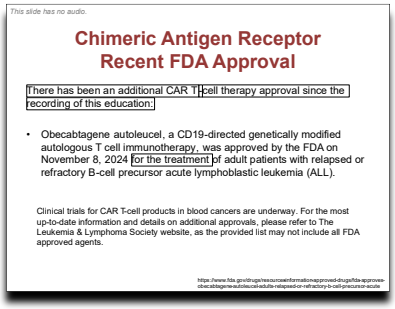


Slide 87: R/R ALL Treatment Options

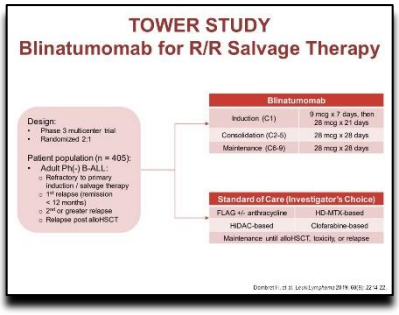
Relapsed/refractory ALL treatments include blinatumomab (Blincyto®), inotuzumab (ozogamycin; Besponsa®), which is a CD22 engaging antibody. Inotuzumab (ozogamycin; Besponsa®), which is also with mini-Hyper-CVAD, so a low-dose, multi, chemotherapy regimen plus antibody therapy. Brexucabtagene autoleucel (Tecartus®) is a possibility, a CAR-T for patients who are B-cell ALL who are relapsed. And for younger patients under the age of 26, tisagenlecleucel (Kymriah®) is another possibility of a CAR-T that's available for this younger patient population.

For B- or T-cell, there's the possibility of a clinical trial. So, if there's a clinical trial available, it's probably one of the more attractive options for this patient population. Augmented hyper-CVAD, clofarabine +/- etoposide, MO-AD, FLAG-Ida or FLAM, high-dose cytarabine (Cytosar®)-containing regimen, or an alkylator combination regimen.

For T-cell disease, we tried to incorporate, if possible — and if the patient can tolerate it —, nelarabine (Arranon®) +/- etoposide, Cytoxan® (cytarabime), bortezomib (Boruzu®) or daratumumab (Darzalex®), mitoxantrone-containing regimen, or a regimen that may contain venetoclax (Venclexta®) plus low-dose multiagent chemotherapy or navitoclax.



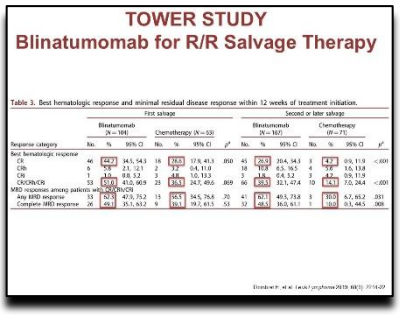
Slide 88: Chimeric Antigen Receptor Recent FDA Approval



Slide 89: TOWER STUDY Blinatumomab for R/R Salvage Therapy

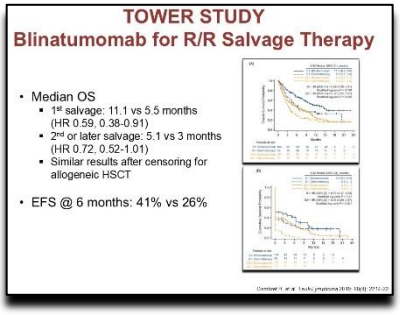
The TOWER study looked at blinatumomab (Blincyto®) for relapsed/refractory disease as salvage chemotherapy. It was a Phase III multicenter trial that was randomized 2:1. It was almost 400 patients with adult Ph-negative B-ALL that were refractory to primary induction therapy or required salvage chemotherapy. For first relapse, remission less than 12 months, or second or greater relapse, or relapse post-allotransplant.

And they received blinatumomab (Blincyto®) as induction, consolidation, and maintenance versus a standard of care of the investigator's choice, including FLAG plus anthracycline, a HiDAC-based therapy, or maintenance until allo stem cell transplant.



Slide 90: TOWER STUDY Blinatumomab for R/R Salvage Therapy

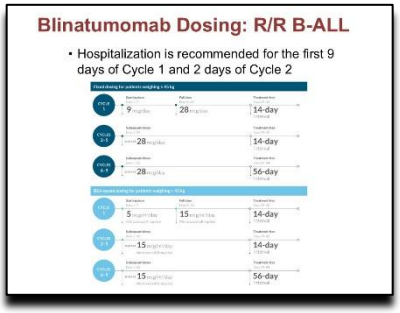
And as you can see sort of in these boxed areas, that blinatumomab (Blincyto®), the CR rate was 44.2% versus multiagent chemotherapy at 28.6%. And the CR, CRh, CRi rate was 51% in the blinatumomab (Blincyto®) group versus 36.5% in the multiagent chemotherapy group. And these were all in patients who received first salvage. The MRD response was 62.3% versus 56.5%, but a complete MRD response was 49% versus 39%. So, it was an impressive showing in first salvage for patients who received blinatumomab (Blincyto®) versus multiagent chemotherapy. For second or later salvage, again, it was in favor of the blinatumomab (Blincyto®) arm at CR rate of 26.9% versus 4.2% in the multiagent chemotherapy arm, and you got a response rate of 39.5% versus 14.1%. Again, there was MRD responses, but most impressive was the complete MRD response was 48.5% in the blinatumomab (Blincyto®) group versus 10% in the multiagent chemotherapy group.



Slide 91: TOWER STUDY Blinatumomab for R/R Salvage Therapy

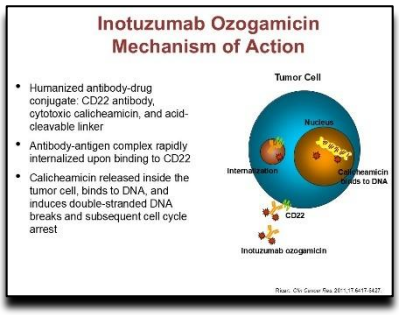
So, in the TOWER study, the median overall survival for first salvage was 11.1 versus 5.5 months, with a hazard rate of 0.59. For second or later salvage, 5.1 versus 3 months — a long way to go, really, still, in improving second salvage for patients. And similar results occurred after censoring for the allogeneic stem cell transplant. Event-free survival, 6 months was 41 versus 26%.

So, first-line chemotherapy-free treatment was associated with a high molecular response and survival, really with minimal toxicity. So, it's a good choice of salvage over multiagent chemotherapy in patients who had not seen blinatumomab (Blincyto®) previously.



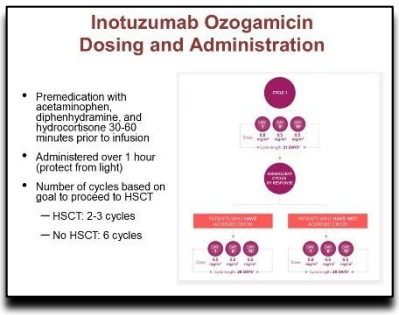
Slide 92: Blinatumomab Dosing: R/R B-ALL

Dr. Johnson: So, when blinatumomab (Blincyto®) is given for relapsed or refractory disease, knowing that patients are starting off with a higher degree of disease burden, it's important that we start them at a lower dose. For our patients who are greater than or equal to 45 kilos, that'll be 9 micrograms. And patients who are less than that, will be 5 mcgs per meter squared per day. After 7 days, assuming that they have no toxicities or tolerance issues, they will be escalated to the full dose, 28 mcgs. Hospitalization for relapsed/refractory blinatumomab (Blincyto®) use requires hospitalization for the first 9 days of Cycle 1 and 2 days of Cycle 2. But other than that, all the same administration, logistics, and toxicities we talked about apply for blinatumomab (Blincyto®) here in this setting as well.



Slide 93: Inotuzumab Ozogamicin (Besponsa®) Mechanism of Action

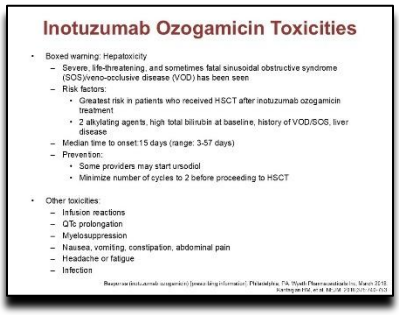
The other novel immunotherapy option that we're using a lot for our B-ALL patients in the relapsed/refractory setting is inotuzumab ozogamicin (Besponsa®). This is a CD22 antibody drug conjugate that's comprised of a CD22 antibody, a cytotoxic calicheamicin chemotherapy, and an acid-cleavable linker. Once the inotuzumab (ozogamycin; Besponsa®) binds to CD22, it's internalized and delivers the conjugated calicheamicin inside the leukemia cells; and it causes DNA double-strand breaks and apoptosis.



Slide 94: Inotuzumab Ozogamicin (Besponsa®) Dosing and Administration

Dr. Johnson: So, when inotuzumab (ozogamycin; Besponsa®) was originally developed, the original dosing strategy was high monthly doses; but the ultimate analog dosing that was formally approved is a fractionated weekly dosing where on cycle 1, day 1, patients receive 0.8 mcgs per meter squared, followed by 0.5 mcgs per meter squared on days 8 and 15. After the 21-day cycle is complete, the dose for Day 1 depends on how the patient responded. So, if they were to achieve complete remission, then they can continue with the 0.5 milligrams per meter squared. But if they have not, then they need to continue with the higher dose 0.8 mcgs per meter squared on day 1 and then the lower doses, days 15 and day 8.

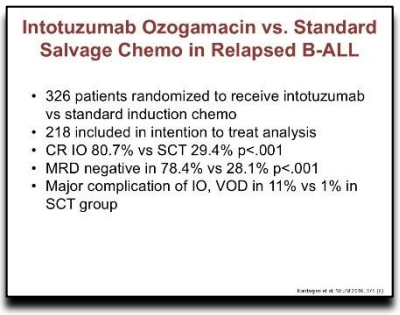
It's given over 1 hour. The duration of inotuzumab (ozogamycin; Besponsa®) treatment really depends on whether your patient is going to allogeneic stem cell transplant. So, if they are, it's really recommended to only do 2 to 3 cycles and allow somewhat of a washout period, and this is to minimize the risk of hepatotoxicity; specifically, veno-occlusive disease, or VOD.



Slide 95: Inotuzumab Ozogamicin (Besponsa®) Toxicities

Severe or life-threatening hepatotoxicity, including VOD, the other name for this is sinusoidal obstructive syndrome. It's a black boxed warning with inotuzumab (ozogamycin; Besponsa®). This occurs due to the calicheamicin component and occurs with or without stem cell transplant exposure. The risk is higher, of course, in patients who've already received a transplant, received 2 or more alkylating agents, have baseline hepatic dysfunction, or disease. Although the median time of onset is 15 days, it can technically occur anywhere in the first 2 months of treatment. So, some providers may give patients ursodiol (Urso®) in an effort to minimize VOD risk. But the most important preventative measure is to reduce the number of cycles and maximize the time

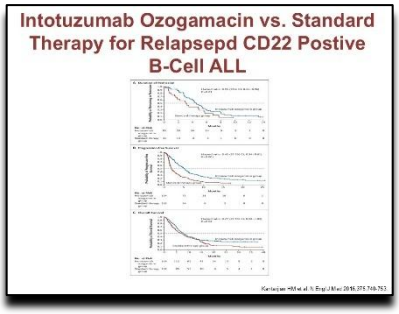
between inotuzumab (ozogamycin; Besponsa®) and transplant. Other notable toxicities include infusion reactions, QTc prolongation, myelosuppression, headache, constipation, and mild nausea and vomiting. Patients should be premedicated with acetaminophen (Tylenol®), diphenhydramine (Benadryl®), and a steroid to minimize the risk of infusion reactions. And, as pharmacists, we should ensure appropriate QTc monitoring is done while also minimizing the use of other QTc prolonging medications.



Slide 96: Intotuzumab Ozogamacin (Besponsa®) vs Standard Salvage Chemo in Relapsed B-ALL

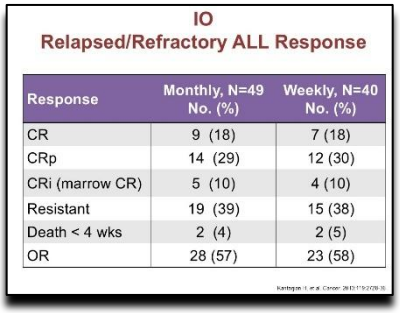
Dr. Ritchie: So, the clinical data looking at inotuzumab (ozogamycin; Besponsa®) versus standard salvage chemo in relapsed B-cell ALL comes from M.D. Anderson. There were 326 patients randomized to receive inotuzumab (ozogamycin; Besponsa®) versus standard multiagent chemotherapy: 218 were included in the intention-to-treat analysis, and the CR rate was 80.7% versus stem cell transplant, which was 29.4% in this patient population.

There was MRD-negativity in 78.4% versus 28.1%. The major complication of inotuzumab (ozogamycin; Besponsa®) was VOD in 11% versus 1% in the stem cell group. So, VOD is a complication we worry about, particularly in patients that we may think about sending to, to stem cell transplant in the future.



Slide 97: Intotuzumab Ozogamacin (Besponsa®) vs Standard Therapy for Relapsed CD22+ B-Cell ALL

You can see that inotuzumab (ozogamycin; Besponsa®) versus standard therapy for relapsed CD22-positive B-cell ALL favors, in the blue line, you can see that is the inotuzumab (ozogamycin; Besponsa®) group versus the red line which is the standard chemotherapy group. And that there is a survival benefit in the inotuzumab (ozogamycin; Besponsa®) group versus the standard chemotherapy group, that basically the lines were very similar, up to 15 months. But after 15 months, there was definitely survival in favor of those patients who received inotuzumab (ozogamycin; Besponsa®).

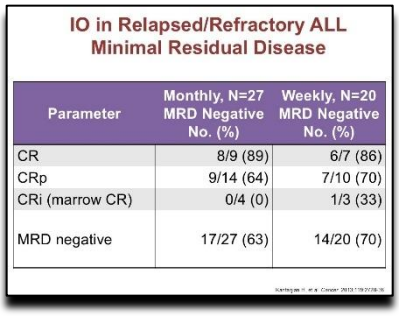

IO
Relapsed/Refractory ALL Response

Response	Monthly, N=49 No. (%)	Weekly, N=40 No. (%)
CR	9 (18)	7 (18)
CRp	14 (29)	12 (30)
CRi (marrow CR)	5 (10)	4 (10)
Resistant	19 (39)	15 (38)
Death < 4 wks	2 (4)	2 (5)
OR	28 (57)	23 (58)

Slide 98: Inotuzumab Ozogamycin (Besponsa®) R/R ALL Response

So, this inotuzumab (ozogamycin; Besponsa®) response for CR monthly versus weekly was very similar again for CRP, for CRi, for resistant disease, and the overall response rate was the same. All 89 patients were evaluable for response, and the response rate for the whole group was 57% and was not different between schedules. However, the fractionated

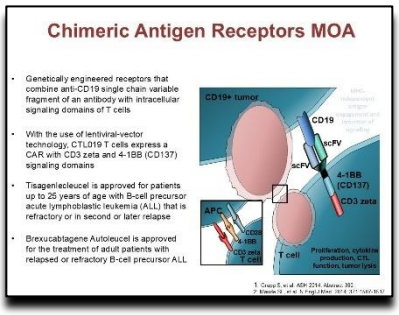
weekly dosing has been mainly adopted as the dosing for patients who are receiving salvage chemotherapy



Slide 99: Inotuzumab Ozogamycin (Besponsa®) in R/R ALL MRD

In inotuzumab (ozogamycin; Besponsa®), looking at the minimal residual disease in these groups was assessed by flow cytometry in 47 of the 51 patients who had a morphologic response, and an MRD-negative status was observed in 66% of the responding patients.

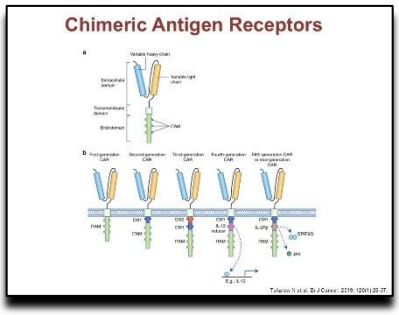
MRD-negativity was rare in the few patients achieving only a CRi. So, if you got a CRi, there was a low chance that you actually were going to become MRD-negative.



Slide 100: Chimeric Antigen Receptors Mechanism of Action

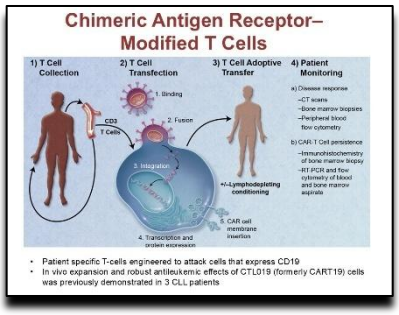
I'm going to talk a little bit now about CAR-T, chimeric antigen receptors. They're genetically engineered receptors that combine an anti-CD19 single-chain variable fragment of an antibody with an intracellular signaling domain of a T cell. And generally they're made by using a lentiviral vector technology, and the CTL019T cells express a CAR with a CD3 zeta and 4-1BB CD137 signaling domains.

Tisagenlecleucel (Kymriah®) is approved for patients up to the age of 25 years with a B-cell precursor ALL that is refractory in second or later relapse. Brexucabtagene autoleucel (Tecartus®) is approved for the treatment of adult patients with relapsed or refractory B-cell precursor ALL.



Slide 101: Chimeric Antigen Receptors

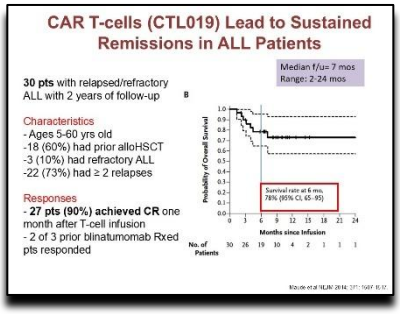
Here is another sort of cartoon of a chimeric antigen receptor, showing essentially variable light chains here, transmembrane domain, and an endodomain. And here is sort of a cartoon of how the CAR-Ts have evolved, from the first generation CAR-T that was relatively simple with the light chain and heavy chain or endodomains, but how they became more complicated structurally over time to be more specific in what sort of reactions and cytokine domains were affected.



Slide 102: CAR–Modified T Cells

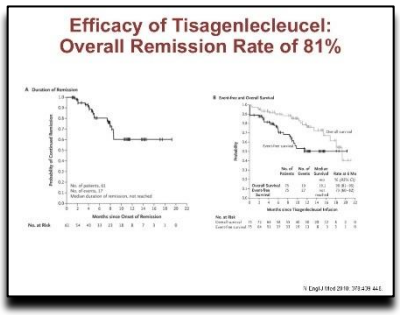
The making of a CAR-T is not a simple process. The first requirement is: T cells are collected from the patient. And those T cells are then engineered to transfect a patient with a treatment that will engage both the T cell and leukemic cell at the same time and induce this adoptive immunotherapy.

It takes a while for all of this engineering to take place. It's then sent back to the treating center and is infused in the patient, and the patient then is monitored over time for toxicity and response. This time period which is taken to create these cells requires that you keep these patients in good enough shape to receive these cells at the other end, which can be weeks at a time, which is a challenge.



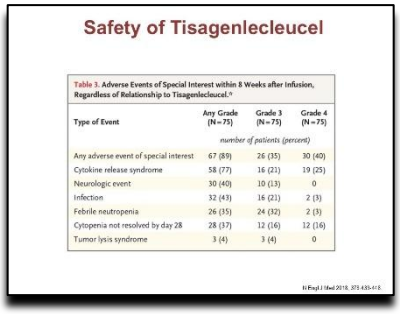
Slide 103: CAR-T Cells (CTL019) Lead to Sustained Remissions in ALL Patients

But if you can get CAR-T cells, they can lead to sustained remissions in ALL patients. This is looking at *The New England Journal of Medicine* paper from 2013 where 30 patients with relapsed/refractory ALL were followed with 2 years of follow-up. These patients were age 5 to 60. Sixty percent had a prior stem cell transplant, 10% had had refractory ALL, and 73% had more than 2 relapses. So this was a poor prognosis group of patients. Ninety percent achieved a CR 1 month after T cell infusion, and 2 of 3 patients who had prior blinatumomab (Blincyto®) responded to treatment. Survival rate at 6 months was 78%. The median follow-up here was 7 months, and the range was 2 to 24 months.



Slide 104: Efficacy of Tisagenlecleucel (Kymriah®): Overall Remission Rate of 81%

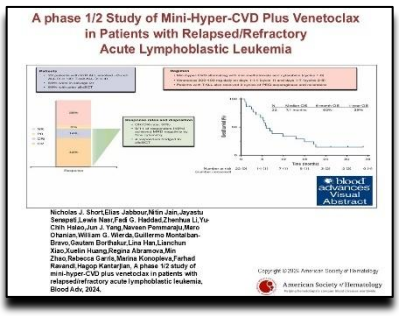
Tisagenlecleucel (Kymriah®), which is the agent approved for younger patients, which is a CAR-T, has an — this is from *The New England Journal of Medicine* paper in 2018. The overall remission rate of patients who receive this was 81% — and looking at overall survival at 12 months, it was essentially 81% versus patients of the event-free survival here, which was about 53%. So, it's an impressive therapeutic option for patients who had refractory disease.



Slide 105: Safety of Tisagenlecleucel (Kymriah®)

The drug has a major toxicity of cytokine release syndrome, which we discussed previously, requiring generally in-hospital treatment. There were neurologic events, but the other events seen were not atypical for patients who have ALL, infection, febrile neutropenia, cytopenias, and tumor lysis syndrome.

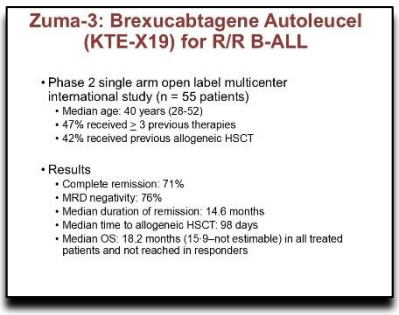
Patients who, are candidates for CAR-Ts generally need to be a healthier type of patient, which is why younger patients are favored here with tisagenlecleucel (Kymriah®); can survive a potential event of cytokine release syndrome or do not have other neurologic comorbidities or tendencies to neurologic comorbidities that would limit treatment.



Slide 106: A Phase 1/2 Study of Mini-Hyper-CVD Plus Venetoclax (Venclexta®) in Patients with R/R ALL

For patients who have T-ALL, there are fewer options for treatment. However, there is the option of using multiagent chemotherapy and adding a BCL2 inhibitor such as venetoclax (Venclexta®). This also can be used in patients who have B-cell disease, but either T-cell or B-cell disease are — patients with refractory T- or B-cell disease are candidates for this treatment.

This is a paper from *Blood Advances* that's relatively recent looking at a small number of patients with refractory disease: 18 ALL patients and 4 T-ALL patients. And many of these, 59%, were in their second salvage or had a prior stem cell transplant. This was, regimen was mini-hyper-CVAD type, alternating with mini-methotrexate and cytarabine (Cytosar®), with venetoclax (Venclexta®) added daily, days 1 through 14 in cycle 1 and day 2 through 8 in cycle 2. Patients with TLL also received 2 cycles of PEG-asparaginase (pegaspargase; Oncaspar®) and nelarabine (Arranon®) in this particular protocol. The response rates — the CRi rate was 57%. And 5 of 11 responders achieved MRD-negativity by flow cytometry. So this is another strategy which can be used in patients who have refractory T-ALL.

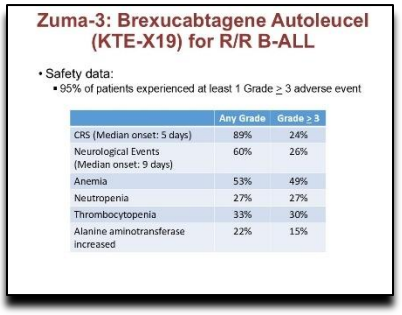


Slide 107: Zuma-3: Brexucabtagene autoleucel (Tecartus®) (KTE-X19) for R/R B-ALL

Another CAR-T was evaluated in the Zuma-3 trial — brexucabtagene autoleucel (Tecartus®), or KTE-X19 for relapsed/refractory B-ALL. This was a Phase II, single-arm, open label, multicenter international study of 55 patients with a median age of 40; and 47% had had greater than or equal to 3 previous therapies, and 42% received a previous allo stem cell transplant. Again, a very poor-prognosis patient population. There was complete remission rate of 71%, an MRD-negativity rate of 76%, the median duration of remission was 14.6 months, and the median time to allogeneic stem cell

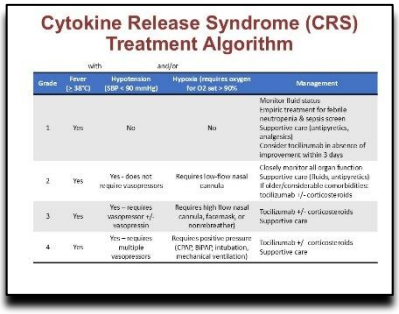
transplant was 98 days. Median overall survival was 18.2 months in all treated patients and not reached in responders.

The major toxicities were CRS again, and this occurred in 89% of patients with a median onset of 5 days. And there was neurotoxicity in 64 and 24% of patients with a median onset of 9 days. So, there were toxicities to this CAR-T just as there had been in prior, but an impressive response rate in patients who had very poor prognosis.



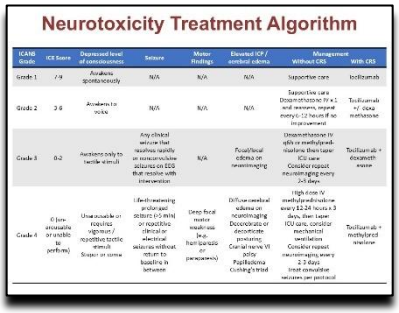
Slide 108: Zuma-3: Brexucabtagene autoleucel (Tecartus®) (KTE-X19) for R/R B-ALL

Again, the safety data, neurologic events were 60%, but 26% of those were Grade 3. CRS, 89%, but only 24% of those were Grade 3 or greater. Anemia and neutropenia and thrombocytopenia are sort of a hallmark of any treatment modality for refractory ALL. And there were some increases in alanine aminotransferase, but generally the drug was reasonably tolerated for the response rate in this poor prognosis group.



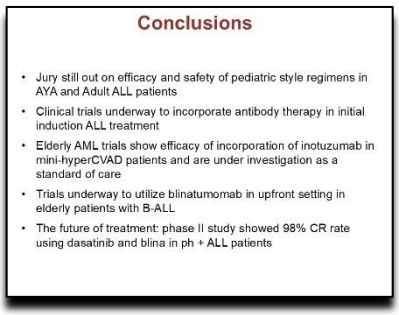
Slide 109: CRS Treatment Algorithm

Again, we discussed earlier the treatments of CRS. This is generally requiring in-hospital treatment with fluids, potentially pressors, potentially oxygen, and potentially IL-6, tocilizumab (Tyenne®), or IL-6 inhibition in corticosteroids. We have sort of a low tolerance for starting these therapies in patients who start to show ongoing symptoms.



Slide 110: Neurotoxicity Treatment Algorithm

Neurotoxicity also, we monitor very closely; and we treat mainly with steroids and again may require in-hospital evaluation and treatment.



Slide 111: Conclusions

We've presented a lot of information today about ALL and about the different treatment modalities which are available. Much is in evolution, really: the value of stem cell transplant in the era of CAR-T, when to initiate antibody therapy, and how to initiate it in frontline consolidation and even maintenance therapy, how are we going to incorporate CAR-Ts in our treatment algorithm of patients long term? Will this become a consolidation or a frontline therapy? How are we

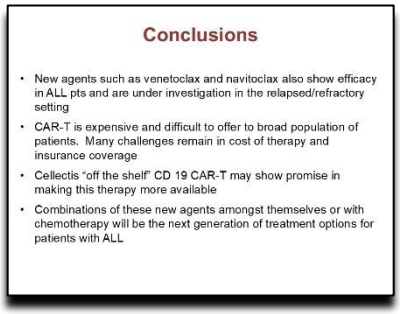
going to treat the elderly population, which does particularly poorly and for which we have no standard of treatment?

So, our conclusions, of our slides today, the jury is still really out on the efficacy and safety of pediatric-style regimens in the young adult and adult ALL patient populations. It's hard to determine whether that higher dose of asparaginase (Rylaze®) is really tolerable in the older group of patients, even though it leads, most likely, to the excellent outcome of pediatric patients with ALL treatment,

Clinical trials are underway to incorporate antibody therapy in the initial induction of ALL treatment. It's not clear how they are going to be used, other than in Ph-positive disease where we've seen really impressive responses using corticosteroids, TKIs, followed by blinatumomab (Blincyto®) treatment as initial therapy for this disease.

Elderly AMLs, trials show efficacy of incorporation of inotuzumab in mini-hyper-CVAD. And this is under investigation as a potential standard of care in this patient population. Trials are underway to utilize blinatumomab (Blincyto®) in the upfront setting, particularly again other than Ph-positive patients, in elderly patients with B-ALL.

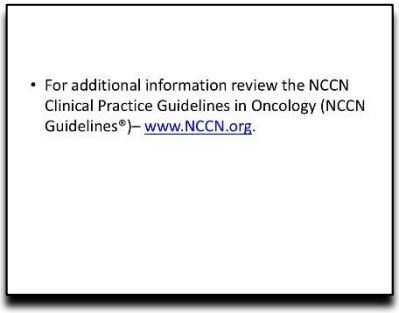
And again, as we discussed, I've discussed above, the future of treatment — certainly the Phase II study showing the 98% CR rate using dasatinib (Sprycel®) and blinatumomab (Blincyto®) in Ph-positive ALL patients is really, really impressive and looks like that is on the road to being the standard of care in Philadelphia chromosome-positive disease.



Slide 112: Conclusions

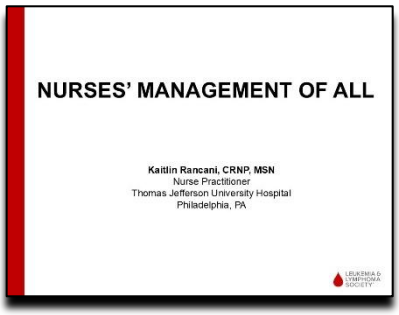
New agents such as venetoclax (Venclexta®) and navitoclax also show efficacy in ALL patients and are under investigation in the relapsed/refractory setting, although data really is only available for a small number of patients. And we'll see how these agents, BLCL2 inhibitors, will be incorporated in treatment going forward. CAR-T is very expensive and difficult to offer to a broad population of patients. Certainly, we find that this modality is extremely effective; but there are many challenges which remain, including the cost of therapy and insurance coverage for this modality. How are we going to pay for this for all of our patients if it becomes something that's used upfront or early in consolidation?

Cellectis is a company working on off-the-shelf CD19 CAR-T therapy, and this shows promise if effective in making this therapy more available, something that can be used earlier in the treatment of this disease and may be more affordable for patients and insurance companies. The combination of all these new agents amongst themselves or with chemotherapy will sort of define the next generation of treatment options for patients with ALL. I think the goal will be to see how many chemotherapy-free regimens can be developed, but incorporating chemotherapy that we have with the newer generations of treatment will probably define the standard of care in the future



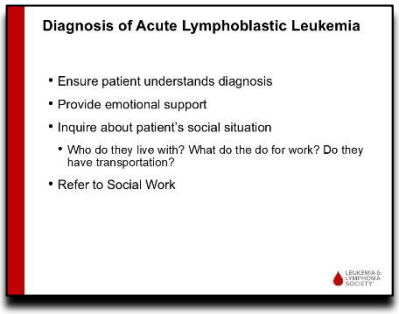
Slide 113: Resources

Thank you all for your attention.



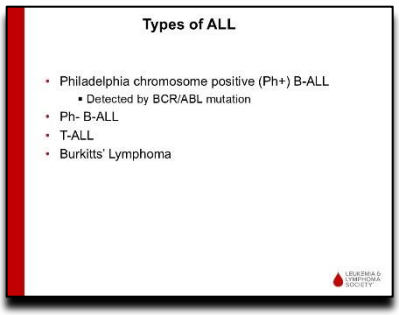
Slide 114: Nurses' Management of ALL

Hi, my name is Kaitlin Rancani. I'm a nurse practitioner at Thomas Jefferson University Hospital. And today I'm going to talk to you about the nurse's management of acute lymphoblastic leukemia, otherwise known as ALL.



Slide 115: Diagnosis of Acute Lymphoblastic Leukemia

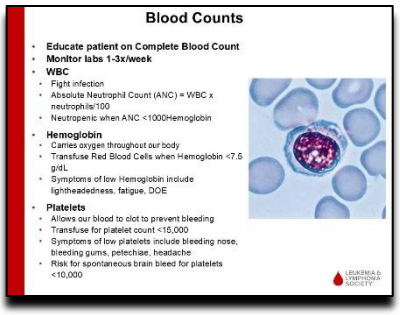
So when a patient is first diagnosed with ALL, it's important to either be there with the doctor while they're providing the diagnosis or go into the room after the patient receives their diagnosis. And you just want to ensure that the patient understands what they've been told and what their disease is; provide emotional support. If you have some time, just inquire about the patient's social situation, such as who did they live with? What do they do for work? And do they have good transportation? And then all patients should be referred to social work. Most importantly, the ones that may have difficulty with transportation or that live by themselves or have financial issues that they would like support with.



Slide 116: Types of ALL

So there's a few different types of ALL, the first being Philadelphia-chromosome-positive, or PH-B, ALL. This is detected by the PCR-ABL mutation. You can detect this on peripheral flow for many new leukemia patients with ALL just because their disease burden is so high. And there is a lot of disease in their peripheral blood to be able to determine which type of leukemia they have. There's also PH negative B ALL, it's B-cell ALL.

Another type of ALL is T-cell ALL, which can be found in the bone marrow, or it can be found in cell areas that form more of solid tumor. And then another form, sometimes subclassified as ALL, is an aggressive type of leukemia, also known as Burkitt's lymphoma, which follows a lot of these similar treatment guidelines due to the same drugs that they get.



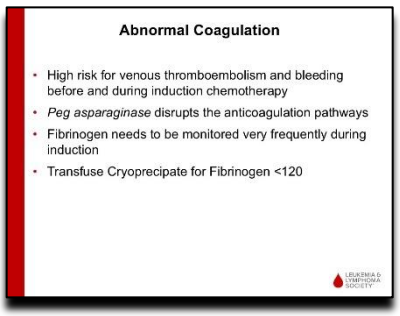
Slide 117: Blood Counts

So with any leukemia, it's important to go over patient's blood counts and make sure they understand their CBC, as this becomes very important during treatment and management of their chemotherapy and supportive care. You have to let them know that you're going to monitor their blood counts one to three times a week. I usually will go over what each cell does.

So a white blood cell helps fight infection. There is a calculation we do to calculate a patient's ANC to determine neutropenia and how neutropenic they are. And, so, this is a calculation of the white blood cell count times neutrophils divided by 100. And if that number is below 1,000, the patient is considered neutropenic. If it's below 500, they're considered very neutropenic. Hemoglobin is what carries oxygen throughout the body. Sometimes patients' hemoglobin oftentimes will drop. We usually transfuse if it's below 7.5. Symptoms of a low hemoglobin can include lightheadedness, fatigue, dizziness, exertion. A lot of people feel weakness in their legs when they're going up the stairs. So if a patient's reporting these symptoms, oftentimes their hemoglobin may be low, and they require a blood transfusion. And then platelets.

Platelets allow our blood to clot to prevent bleeding. We usually transfuse platelets if a platelet count is around 15, depending on your institution's guidelines. Symptoms of low platelets can include a bleeding nose, bleeding gums, petechiae. It can include a headache. If a patient's platelets are below 10,000, they can be at risk for a spontaneous brain bleed, which would be a medical emergency.

So we really want to monitor patients' platelets closely when they're dropping after chemotherapy or with disease to help mitigate the risk of a brain bleed.



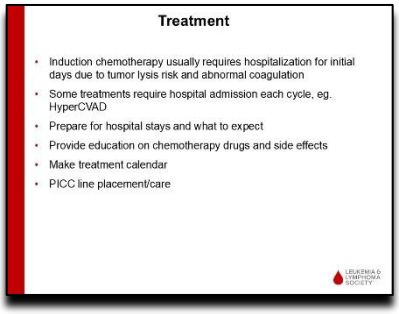
Slide 118: Abnormal Coagulation

Something unique to ALL is also a patient can have an abnormal coagulation on diagnosis, and especially during the first cycle of treatment. So they're at very high risk for both blood clots and for bleeding before and during induction chemotherapy. There is one drug that's given to ALL patients if they're below the age of 55 called PEG-asparaginase [pegaspargase] (Oncaspar®).

This drug in particular disrupts the anticoagulation pathways. So it's very important to monitor a patient's fibrinogen. Sometimes this needs to be checked daily. You'll kind of get the feel of what the patient's trending like. But we usually transfuse cryoprecipitate for a fibrinogen less than 120. And that's mostly in the outpatient setting just to hopefully not have the patient come every day.

If it's inpatient, sometimes they have a lower threshold, but this is to prevent any bleeding.

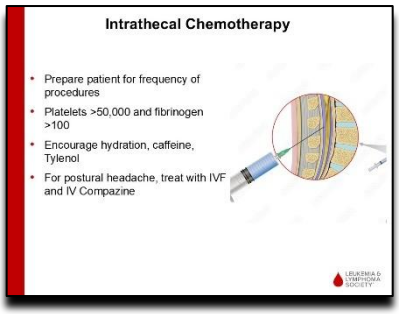
This is most profound during induction, but every time a patient does get PEG-asparaginase [pegaspargase] (Oncaspar®), it's important to monitor their fibrinogen following treatment. They could still need cryoprecipitate in future courses of therapy; however, they probably will need it much less frequently.



Slide 198: Treatment

So, for treatment, most of the time, patients are diagnosed with acute lymphoblastic leukemia actually when they're in the hospital, because it is kind of an aggressive leukemia. Patients become really sick, and they end up in the hospital, which is where they usually get their diagnosis. If they are in the outpatient setting, oftentimes, we have to admit them for their induction chemotherapy. And this is usually because they're at high risk for tumor lysis, or they can have abnormal coagulation problems. So just for the first week, it's good to have them inpatient just for close monitoring. Some treatments require hospital stays with each cycle of treatment. For example, a regimen called hyper C-VAD every 21 days, the patient has to go into the hospital. Also, with some of the Burkitt's lymphoma patients, have to go into the hospital with their treatment. It's important to prepare the patient for what to expect during their hospital stay, how long they're going to be there, what they should bring with them, what to expect on discharge, and what appointments they'll need to come back for. You want to provide education on all the chemotherapy drugs and their side effects.

Making a treatment calendar is really important for ALL patients. These regimens are really intense and very busy. It's hard to understand the pattern to them. So making a treatment calendar for them can be really beneficial. And oftentimes a pick line is recommended.



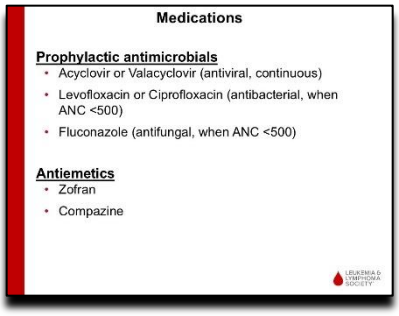
Slide 120: Intrathecal Chemotherapy

One other thing unique to ALL is that there's a high risk for CNS disease. So that's leukemia that enters the CSF fluid. So to prevent that from happening, patients need often 8 to 12 intrathecal chemotherapy procedures during the course of their treatment. So you want to prepare them for the frequency of these procedures.

Sometimes it's challenging in induction therapy because they do need a platelet count of 50,000 and fibrinogen should be above 100 in order to perform the procedure of a lumbar puncture. You don't want to have any risk for bleeding. So if treatments have to be delayed, that's usually fine. After a patient has the intrathecal chemo performed, you want to encourage hydration, caffeine, Tylenol® [acetaminophen].

You know, you take out cerebrospinal fluid and we test, we know we send that off to pathology for testing and we replace the fluid with the chemotherapy. So we try to balance the spinal fluid. However, sometimes that balance isn't perfect and patients can get severe postural headaches. If it's really severe, you can bring them to the infusion center and offer

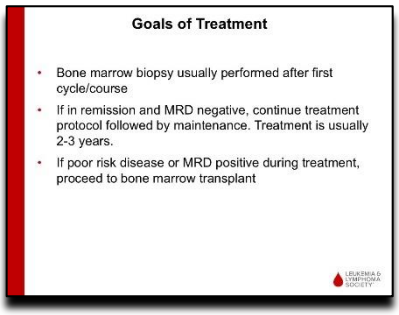
a liter of fluids and IV Compazine® [prochlorperazine], and that usually does the trick. Worst case, patients get referred for a blood patch.



Slide 121: Medications

So medications that are used during the treatment of ALL are preventative antibiotics. We give valacyclovir (Valtrex®) or acyclovir (Zovirax®). This is an antiviral. They take it all the time. This helps prevent shingles. For antibiotics, use levofloxacin (Levaquin®) or ciprofloxacin (Cipro®) for an ANC less than 500. This is to prevent an infection.

And then for their antifungal prophylaxis, they can just take fluconazole (Diflucan®) when their ANC is less than 500. The duration of neutropenia is often a lot less of a time period than AML. So fluconazole (Diflucan®) is sufficient coverage for antifungal prophylaxis. And then the frequent anti-emetics that we use are Zofran® [ondansetron] and Compazine® [prochlorperazine]. It is possible to do other anti-emetics if needed, such as Zyprexa® [olanzapine] or Ativan® [lorazepam], Phenergan® [promethazine], you know, whatever will work for the patient.

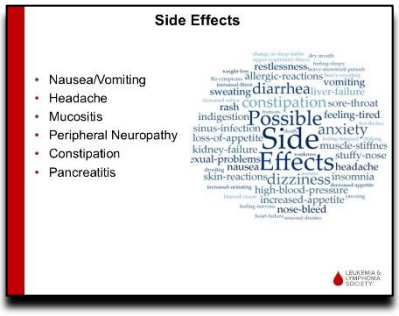


Slide 122: Goals of Treatment

So the goals of treatment, of course, are to get the patient into remission. We usually perform a bone marrow biopsy after the first cycle or first course. If the patient is in remission and MRD-negative, which is minimal residual disease, then they can continue their treatment protocol followed by maintenance therapy. The treatment is usually over a course of two to three years.

There are few regimens. It's hard to go into detail for each one, but it is a long course of treatment. The first, say, four to six months is kind of more of an aggressive, intensive treatment. And then all patients with ALL usually proceed to maintenance therapy, which is usually monthly treatment, sometimes with oral medications.

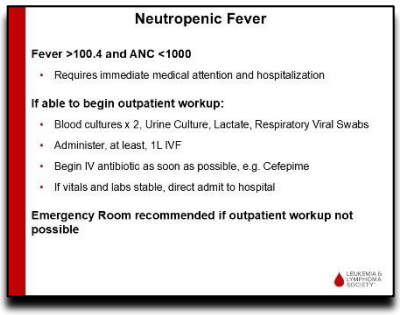
If a patient's at poor risk, has poor risk disease, or is MRD-positive during the treatment, then those patients usually proceed to have a bone marrow transplant, if eligible.



Slide 123: Side Effects

So some side effects that come with the treatment of ALL are common ones that we think of, such as nausea and vomiting, headache, especially from the lumbar punctures and intrathecal chemo. Mucositis can occur. Peripheral neuropathy is a big one because vincristine (Oncovin®) is administered so frequently during treatment. So it's really important to check in on patient symptoms of numbness and tingling in their fingertips and toes.

Vincristine (Oncovin®) also causes constipation, as does Zofran® [ondansetron]. So it's important to make sure they're moving their bowels regularly. And another unique side effect with ALL treatment, mostly due to the PEG-asparaginase [pegaspargase] (Oncaspar®) that patients are receiving that is pancreatitis. So if they develop this sudden abdominal pain, it's important to rule out pancreatitis.

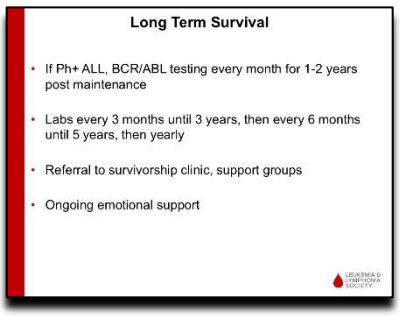


Slide 124: Neutropenic Fever

As with AML, ALL, you know, puts you still at risk for neutropenic fever when your blood counts drop. So it's really important to educate patients to be checking their temperature at home at least twice a day or if they're not feeling well. If a patient develops a fever over 100.4, they should call the office and come in for an office visit right away. If it's after hours, they should go to the hospital.

If you're able to begin an outpatient workup for a neutropenic fever, you want to make sure you do blood cultures, a urine culture, a lactate, respiratory swabs. You can administer at least a liter of IV fluids, sometimes more if their vital signs are unstable. You want to begin an IV antibiotic as soon as possible. And as long as they're otherwise doing, you know, feeling stable, you can directly admit them to the hospital.

However, if they're unstable or the outpatient workup is not possible, they should proceed to the emergency room.



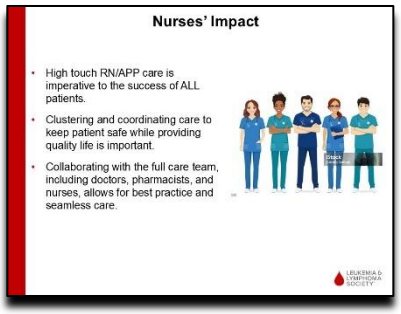
Slide 125: Long Term Survival

So long-term survival, if a patient has Philadelphia-chromosome-positive ALL, you want to do BCR-ABL testing every 1 to 2 years post maintenance therapy, just to monitor that they're still remaining in remission. Mostly, labs are done every 3 months for 3 years, then every 6 months after that, and then after five years, you can have yearly exams and blood work.

You want to make sure you refer patients to the survivorship clinic and any support groups necessary. They also need a lot of ongoing emotional support. So, ALL is, like I mentioned before, sometimes very aggressive. The treatment is really intense. Patients are not feeling well. They can be in and out of the hospital. It's kind of a whirlwind and a lot of, you know, fight or flight mode. So, sometimes when they're coming down off treatment, that's when a lot of their anxiety and emotion can actually heighten. So making sure they have good support is really important.

And as with all acute leukemia, it's a — high-touch care for the patients is critical to the success of these patients. You want to try and cluster and coordinate their care as much as possible to allow some convenience in their life and quality of life. However, you want to make sure you're monitoring, you know, the appropriate things closely and that they're

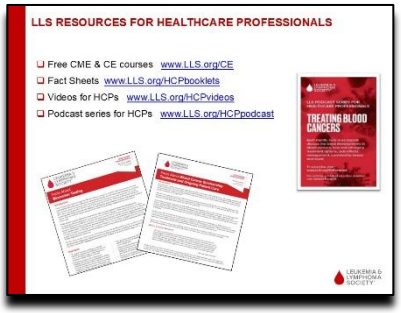
staying safe.



Slide 126: Nurses' Impact

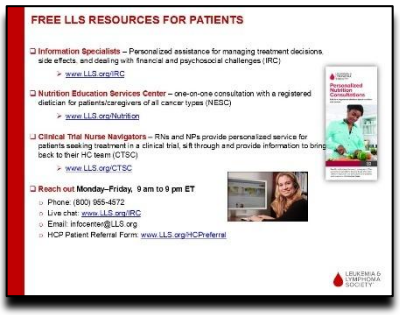
So in closing, collaborating with the full team of doctors, pharmacists, nurses allows for best practice and a seamless care. These patients are really special. They do require a lot of care. They can get really sick, but they can also get better and be in remission and go on to live a long, full life.

So this is the end of the presentation. I hope it was helpful to you and thank you.



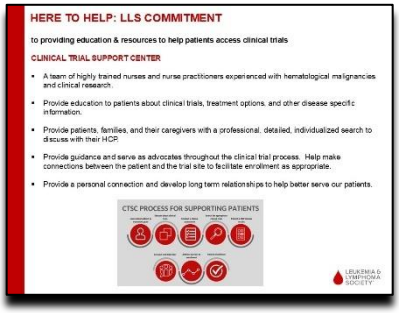
Slide 127: Free LLS Resources for Healthcare Professionals

Thank you to our faculty for your informative and interesting presentations. I am now pleased to share brief information about resources for you and to share with your patients. The Leukemia & Lymphoma Society offers free CE and CME online webinars such as this one, in-person regional programs, and a podcast channel for Healthcare Professionals, where you can listen to discussions on treatment, side-effect management and more. New and interesting topics are added every few weeks. Access these, as well as videos and fact sheets for Healthcare Professionals at the link on this slide.



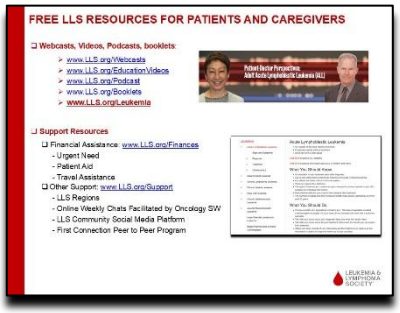
Slide 128 Free LLS Resources for Patients

LLS Information Specialists are highly trained Oncology Social Workers and Nurses who provide accurate, up-to-date disease, treatment & support information, including financial, in one to one conversations with patients. Patients can contact them directly, or you can complete a referral form. They can also help you order free copies of booklets to give to your patients. LLS offers free nutrition consultation to patients and caregivers with any cancer diagnosis in a 30-minute phone call with one of our registered dietitians. Contact them using the info listed here to refer a patient. Our Clinical Trial Support Center Nurse Navigators are RNs and NPs with expertise in blood cancers. They work 1 on 1 w/patients, via telephone, to provide user friendly information, help find appropriate clinical trials, personally assist them throughout the clinical trial process and provide info for the patient to bring back to their healthcare team. They also work with Healthcare Professionals. This is a unique service from LLS. I hope you will consider all of these specialists as an extension of your team.



Slide 129: Here to Help: LLS Commitment

Here is a brief overview of the Clinical Trial Support Center process for supporting patients. The goal is not to enroll every patient into a trial, rather to increase opportunities for participation by facilitating informed decision making and minimizing logistical barriers for the patient. They work in collaboration with the patient's healthcare team to decide if a clinical trial is right. Ultimately, they educate, support, and empower patients to be active participants in and have control over their treatment decisions.



Slide 130: Free LLS Resources for Patients and Caregivers

LLS offers blood cancer disease specific information and support resources for patients and caregivers, including telephone and web education programs, videos, podcasts and booklets. I encourage you and your colleagues to stay up to date on the availability of LLS' Financial Assistance programs, and other resources, using links in these slides.

Slide 131: Free LLS Resources for Your Patients

We are committed to addressing needs of minoritized & underserved communities impacted by a blood cancer, including those facing barriers to optimal care. Our booklets are available in English and Spanish and our Information Specialists, Clinical Trial Nurse Navigators, and Registered Dieticians, consult with patients in several languages.

Slide 132: Thank You!

Thank you again to our faculty and thank you to all the healthcare professionals listening. I hope the information will be helpful to you, as you care for your patients. If you would like more information for yourself or support for your patients, please contact an Information Specialist at The Leukemia & Lymphoma Society at 800.955.4572 www.LLS.org/support.