

**Frontline Updates From the Annual Hematology
Meeting: Advances in the Treatment of Acute
Leukemia**

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DR. WILLIAM MENCIA: Hello, I'm Dr. William Mencia and welcome to Med-IQ's coverage of the 2013 American Society of Hematology annual meeting. I'm joined today by Dr. Scott Howard of St. Jude Children's Research Hospital. Welcome Scott.

DR. SCOTT HOWARD: Thank you very much.

DR. MENCIA: A lot of data are being presented at this meeting on acute leukemias. What trials have captured your attention so far?

DR. HOWARD: This has been the most spectacular ASH ever, and there are so many clinical trials, pre-clinical trials, and basic science. I'd have to say that we really have A-plus outstanding research presented in clinical areas and in scientific areas and the wedding of the two.

DR. MENCIA: How will all of this translate into further management of acute leukemias?

DR. HOWARD: I see it as two categories. The first category is basically a better use of what we already have available, and one example of this is asparaginase. It's been around for four decades, but there are still only 30, 40, maybe 50 abstracts about different ways to use asparaginase. The second category is new stuff, new medicines, new combinations of medicines, and adding a new medicine to an old backbone. I guess those two major categories sum up 80% of this meeting and then 20% is a third component, which is also critical—how you would apply all this to a modern-day practice and how you would integrate a staggering amount of new information into the day-to-day practice. They even had a session about how to do a guideline, how to interpret a guideline, how to use a guideline, and how to deliver care in a way that's adequate. However, I think the most important thing is how we would use existing medications better because that's something we could start today.

DR. MENCIA: That's an interesting concept—better use of approved medications. Can you elaborate on that?

DR. HOWARD: Definitely. For example, acute lymphoblastic

leukemia, the most common childhood cancer, is also very common in adults. We know how to use the standard medicines asparaginase, mercaptopurine, and daunorubicin. Yet, only this week, it was reported that Down syndrome patients in the UKALL 2003 trial experienced much higher toxicity. In fact, they lost 10 out of the first 41 patients and had to make a dramatic modification in the therapy. Well, not dramatic, it's actually sort of a light modification using a 3-drug induction—taking out one of the delayed intensifications and shortening the maintenance down to 2 years; all of a sudden the Down syndrome patients now can do as well as the other patients. This is an example of adapting existing medications to a new patient group that is now recognized as a special group that needs some special care.

Other examples are Philadelphia chromosome-positive ALL, which accounts for 2% or 3% of children with ALL and 25% to 30% of adults with ALL. Adding the tyrosine kinase inhibitors imatinib or dasatinib to the backbone therapy has transformed the care of these patients and is now to the point where transplant is not even necessary for Philadelphia chromosome-positive ALL, whereas before it was almost mandatory. I think there are probably 50 examples that were presented, but we could also think of adapting a chemotherapy regimen, for example one that was piloted in children, and use it in adults. This is the prototype in acute lymphoblastic leukemia, once again, and they call it a pediatric-inspired regimen, which means a long maintenance, delayed intensification, and intensive use of asparaginase and some other component of CNS control. The question was, though, could a pediatric regimen be tolerated by older people and especially older adults? Maybe they would have more comorbidities and more additional medications that they would already be on so that it wouldn't be as easy for them to finish the treatment. It was really nice to see the 10403 study come out; it had a very clever design because it compared the pediatric regimen. It used a virtually identical regimen but in older patients aged 16 to 39 instead of aged 0 to 18. It compared the teenagers in this group with the teenagers on a COG protocol, the 0232 protocol, and also compared the older patients (aged 21 to 39) with the teenagers.

The bottom line was that the pediatric regimen worked equally well in people aged 21 to 39 as in people aged 0 to 20, and the toxicities were not exactly the same but were comparable—nothing surprising.

DR. MENCIA: Let's change our focus now and talk a little bit about stem cell transplantation. What data have been emerging out of this meeting with regard to complete response or partial response?

DR. HOWARD: It's beyond the scope of our segment to talk about how stem cell transplantation has improved in the past year, but there have been fantastic improvements in that. I'd rather talk about how we prevent the need for stem cell transplantation in the first place, and that is through the use of more effective chemotherapy. More effective chemotherapy includes adding imatinib or dasatinib at baseline to the base chemotherapy for ALL, using targeted agents, and using new agents for relapse so that transplant will be unnecessary when those therapies become frontline and achieve deep remission. So, at this time, I would say that transplant in first remission is almost never indicated for adults or children with ALL. That's a major paradigm shift in the management of ALL.

DR. MENCIA: We're also seeing a lot of data coming out regarding newer formulations of some of the older medications. What information have you found to be interesting?

DR. HOWARD: There's a wealth of information on this category too, so interesting, that includes liposomal doxorubicin and putting the same old medicine into a liposome so that it gets to the tissues that it's supposed to get to and avoids the tissues that it's not supposed to get to, like the heart. It's already improved care for people with all kinds of cancers, particularly acute leukemias. If we think of this strategy, liposomal vincristine has several interesting abstracts. In one of them, they escalated the dose of liposomal vincristine. This was presented by Dr. Deitcher, and the higher dose was very well tolerated. Neuropathy was still less than with naked vincristine, and the hematologic toxicity was practically nonexistent.

Again, this is an example of the same old medicine being

used. Vincristine's been around for many decades, but now liposomal vincristine allows administration at a much higher dose with less toxicity. We can think of other types of repackaging strategies. One is a liposome. Others include nanoparticles or pegylation of the molecule. The one abstract on nanoparticles used something called SHELS, S-H-E-L-S, and I like the name because it involves the synthetic hollow enzyme loaded porous nanoshell. Within the shell you package whatever drug you want, in this case asparaginase, and the reason that's important is because the shell essentially protects the drug from the immune system. One of the limiting toxicities of asparaginase is an allergic reaction, but, if the immune system can't detect the asparaginase, the asparaginase continues to have it's activity but with no immune reactions—no neutralizing antibodies.

The experiment they did was fantastic because they basically first put the asparaginase into the shell and then put the shell into some mice. The shell depleted the asparagines as well as the normal asparaginase that was not in the nanoparticle. Then, to really prove the point that the asparaginase is protected from the immune system, they immunized the mice against asparaginase. The mice had high titers and neutralizing antibodies. So, when they gave the asparaginase naked, the neutralizing antibody that clears it from the system had no effect. When you give the asparaginase in the shell, the shell protects it and it has the same effect in a patient as in a mouse with no neutralizing antibodies. We can imagine a future where even a very old medicine like asparaginase—I think it came out in the early seventies, late sixties—can be delivered, even to an allergic patient, by putting it into a nanoshell and letting it just float around there in the shell and do its job. So, there are some very clever drug combinations and new technologies under development to make old drugs even better and to make the new drugs better too.

DR. MENCIA: Of course, as we can imagine, a lot of these data are being looked at in the preclinical stage, at the clinical stage; what's ready for prime time now? What do you think in the near term will start impacting clinical practice?

DR. HOWARD: That's a great question. Right now, today,

immediately, we can make better use of approved medications. For example, today, we can use a pediatric-inspired regimen in a 30-year-old with ALL. Today, we can add tyrosine kinase inhibitors to ALL therapy; it's already being done. Many ongoing trials and standard-care regimens would include a tyrosine kinase inhibitor in a patient with Philadelphia chromosome-positive ALL. Also, today, we can use approved medications in our new subgroups of ALL. For example, Philadelphia-like ALL is a new group that's not Philadelphia chromosome-positive but has in many cases a sensitivity to the tyrosine kinase inhibitors. So, we could imagine identifying those 3%, 4%, or 7% of patients who are Philadelphia-like and suddenly improve their cure rate by 30% or 40% just by adding approved medications.

We also can use antibodies. The antibodies got a lot of attention these past few days, including the naked antibodies—rituximab against CD20, pertuzumab against CD22, or alemtuzumab against CD52. Naked antibody just means an antibody alone—the antibody binds to the leukemic cell, and the immune system kills the leukemia. There are also some very clever new antibody designs like the bispecific BiTE antibody, which is a bispecific single-chain antibody. This type of antibody, blinatumomab for example, acts against CD19. Fortunately, almost all B-cell ALLs are CD19-positive, so it's pretty good for most B-cell ALLs. This antibody essentially makes the T cells attack the CD19 cells, so that's why it's a bispecific antibody—because it binds to the target leukemia cell and then attracts the T cells to make the attack.

There are also other categories, such as immunoconjugates or immunotoxins. One immunoconjugate is inotuzumab, which is a CD22 antibody combined with ozogamicin. We have something just like it for AML—a CD33 antibody combined with ozogamicin called gemtuzumab ozogamicin. So now we essentially have a gemtuzumab ozogamicin for ALL because it's attacking CD22, releasing the ozogamicin to then kill the cell. Perhaps the newest and maybe the most exciting are the chimeric antigen receptors—the CAR therapies, and maybe we have time to talk about a couple of those.

DR. MENCIA: Along those lines, were there any abstracts presented at this meeting that really stuck out to you that

bring some perspective to the use of these antibodies?

DR. HOWARD: For sure, there were quite a few abstracts on blinatumomab—in adults and children, in massively refractory ALL versus first relapse of ALL, and in phase 1 and phase 2 studies. For example, Arend von Stackelberg from Virchow presented one on a phase 1/2 study of blinatumomab for children with ALL, super refractory ALL, and one, two, or three relapses, however many. It was basically a dose-finding study, standard phase, one design. They started with 5, 10, 15, 30 µg. At 30 µg the dose-limiting toxicity was too much, and the dose-limiting toxicity was interesting because of an old disease tumor lysis syndrome, which means you killed the cancer too fast and now the byproducts are spilling into the system and have to be metabolized. If the body can't handle it, then acute kidney injury and other results of tumor lysis syndrome occur.

Now here we have cytokine release syndrome, which essentially means that the immune system attacks the leukemia so fast that the leukemia is broken apart, releases cytokines, and the immune system releases cytokines. If there's too much leukemia combined with a too-effective therapy, we get both cytokine release syndrome and tumor lysis syndrome. It turned out that this was dose limiting for blinatumomab, because it was so effective. The study currently is at a phase where they're starting with 5 µg and then escalating the dose within that patient, as the tumor burden goes down, to 10 µg and then to 15 µg. So, instead of saying that the dose-limiting toxicity is 15 or 5 or 10 µg, they say that the initial dose should be 5 µg and then it will be increased to 15 µg to get the maximum efficacy.

Again, it's a clever adaptation of the phase 1 design to start with whatever dose you need to get the initial response and then increase the dose to get the maximum response. The great thing is that many of the patients actually went into remission, so even in a phase 1 study we actually saw some good clinical results in addition to finding out the safe and effective dose.

DR. MENCIA: That's fascinating. We've reviewed an overwhelming amount of information today. Can you bring it home for us?

What are your take-home messages if we're out in the community as practicing hematologists and oncologists? What are the take-home messages in acute leukemia?

DR. HOWARD: I think the first and most important message is to have high respect for existing medications, because we've come a long way with what's been done over the last 50 years and are still remixing things into a better protocol. If a pediatric protocol works for young adults, then adapting it to young adults. Learning that pediatric protocol is a really worthwhile exercise, so I think that investing a few hours to get up to date on existing strategies for patients will improve healthcare more than anything else today. One to 3 years from now, I think we'll see most of these antibodies in standard use in adults and children with ALL, especially those with relapsed and refractory ALL. Also, we can't give up on developing new things, new packaging for old medicines, and brand new medicines. That leads me to maybe the most exciting thing that I saw this week, which is the use of CARs—chimeric antigen receptors. In one case from Sloan Kettering, they presented an antibody that's a combination of CD19 (binding domain) and CD28 (co-stimulatory receptor) so it's a chimeric antigen receptor (19-28z CAR). CD19 binds to the leukemia but then CD28 and the zeta group of the CD3 makes it massively activate T cells. Those T cells then destroy the leukemia, so I would say it's another case of using a new medicine on an old immune system that has been around for millions of years. So now we're using something a million years old and something developed recently to attack the leukemia cell through a clever combination of immunology, oncology, smart thinking, smart science, and smart medicine. I think we have a lot we can do today to help patients, and we have a lot we'll be able to do in 6 months, 12 months. I think that the next ASH meeting is a must-attend event because I suspect that there is going to be an exponential growth of really effective and incredibly clever and potent use strategies.

DR. MENCIA: That's exciting information. Thank you Scott. I want to take this moment to appreciate your insights and to thank you for your time today.

DR. HOWARD: It's a pleasure and thank you for having me.