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Should all fit, newly diagnosed patients with AML receive 3+7 based induction therapy?

Welcome to *Managing AML*. I am Dr. Richard Stone. I am frequently asked, "Should all fit, newly diagnosed patients with AML receive 3+7 based induction therapy?" That is a very interesting question. It's a question that I would never have been asked a few years ago, because it was pretty much of a reflex by leukemia treaters that if a patient was fit of any age – even up to age 75 or 80 in some cases – if they had AML and it wasn't acute thrombocytic leukemia, they would receive 3 days of anthracycline (such as daunorubicin) and 7 days of continuous infusional cytarabine. That was the story, and we would try to get them into remission. Remission would be measured by morphologic analysis of their bone marrow and blood approximately 4 to 6 weeks after the therapy. We would want to see less than 4% blasts in the marrow. We would want to see recovery of normal hematopoiesis.

As it turns out, not all fit patients treated with 3+7 benefit from 3+7. I would like to call your attention to a group of patients with intrinsically resistant disease, namely those with complex cytogenetics, and/or a 3q26 cytogenetic abnormality, and/or translocation between chromosome 6 and 9, and/or a TP53 mutation. These patients have a low response rate to 3+7 chemotherapy. Moreover, they have a very poor long-term event-free survival with 3+7 chemotherapy. These types of intrinsically resistant patients simply do not respond well to chemotherapy. Now, this is controversial, but I would consider giving such patients hypomethylating agent-based therapy, and the data for that comes from a couple of sources. One is the AML-001 trial conducted in Europe led by Dr. Hervé Dombret. The trial randomized patients who were older who had lower white counts (less than 15,000 at diagnosis) to either azacitidine for 7 days every month, or what was called conventional care therapy. This could include a pre-selected choice between supportive care, low-dose ara-C, or 3+7. Now most of the patients did not get 3+7, but in that trial, people did just about as well if not a bit better by having been randomized to the hypomethylating agent therapy. So, that was one piece of data supporting the use of hypomethylating agent therapy even in people who might be considered fit for 3+7.

The second piece of data which I really find intriguing was recently published in the *New England Journal of Medicine* by Dr. Welch of Washington University in St. Louis. He treated a group of patients with AML with 10 days of decitabine, and he noted that the response rate of people who had TP53 mutations, generally considered to be a horrible prognosis, was virtually

100%. Now, these people weren't all cured. Some of them were able to go to transplant and some were not, but it seems like low-dose therapy might be better, or at least no worse, than the standard 3+7. That is something to consider for our highly adverse biological type of AML patients almost regardless of their age, but these are more common in older adults.

Secondly, I would like to call your attention to a very interesting new drug called CPX-351 or VYXEOS which is going to hopefully be approved in a certain subset of AML patients. That subset will be AML patients who have had a history of a prior myelodysplastic syndrome, or who have bad chromosomes or dysplasia in the marrow at the time the AML was diagnosed. This is generally referred to as secondary AML, though it is a bit more complicated than that. CPX-351 is daunorubicin and ara C, but it is enclosed in a lamellar capsule, in a sense, which allows a fixed molar ratio to be delivered hopefully to the leukemic stem cells. A phase 3 trial reported by Dr. Jeffrey Lancet at ASH about a year and a half ago showed that CPX-351 was superior in terms of overall survival, versus standard 3+7 in this specified group of AML patients. I think that is going to be something we are going to have to think about for this subset of AML patients in the very near-term future. Again, this is daunorubicin and ara-C, but it is not 3+7; it is a new way to deliver the same drugs. In summary, I would support a careful analysis of the intrinsic biologic leukemia risk of the patient at the time of diagnosis, and may be consider not using 3+7 for people with a really bad risk, and in the near future perhaps considering CPX-351 for patients with secondary AML. Thank you for viewing this activity.