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Risk-Stratification in Newly Diagnosed CLL

Announcer:
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Dr. Kipps:
Hello, this is CME on ReachMD, and I'm Dr. Thomas Kipps at UC, San Diego. And I'm here to talk about risk stratifications for patients with chronic lymphocytic leukemia.

There are 2 major risk classifications that I wish to cover today, and one is designated the CLL4 category of risk stratification, and also the CLL International Prognostic Index. They're very similar, but they do have some key differences. Both have value in predicting the time from diagnosis to the initial treatment, as well as the treatment outcome.

The CLL4 uses 4 major risk factors, one to look at the elevation and lactic dehydrogenase, the other is to look for elevation in serum beta 2 microglobulin levels exceeding 5 mg/L.

Another is for TP53 mutation, with deletion in the short arm of chromosome 17, or deletion 17p, or mutations in TP53. And the final one is relapsed disease. Each of these 4 risk categories scores one point. So, for example, a patient with elevated LDH and elevated beta 2 microglobulin level without TP53 mutations or relapsed disease would score 2 points on the CLL4 category. Higher scores that you have indicate increased risk, and so this is important to know.

The CLL International Prognostic Index, or IPI, actually has 5 factors. They consider age, which is anybody over 65 years of age. They also consider clinical disease status, either an A-, B-, or C-stage disease, or Rai 3 and 4 stage, or 1, 2, 3, 4 stage. If you have, also, mutations in TP53 or they look at the mutation status of the antibody that's expressed by the leukemia, whether it's mutated or unmutated. The IPI also includes consideration of the serum beta 2 microglobulin level, including a cutoff of 3.5 mg/L.

Now, for each of these categories, they're not weighted equally. Age will score as 1 point if you're over 65. You'll get 1 point if you're stage B or C, or stage 3 or 4 in the Rai classification. If you have TP53 mutation, you will score as 4 points. If you have unmutated antibody genes expressed by the leukemic cells, you score as 2 points. If you have elevated beta 2 microglobulin levels over 3.5 mg/L, you also score 2 points.

One consideration, because beta 2 microglobulin is an element in each of these prognostic indexes, you have to remember that beta 2 microglobulin levels can be influenced by the renal status. So those patients who have defects, decreases in their glomerular filtration rate may have elevated beta 2 microglobulin levels as a consequence of this.

Now, both of them appear to help in predicting 5-year progression-free survival in the era of chemoimmunotherapy and the CLL4 trial identified 3 risk groups with 5-year progression-free survival of 0%, 12%, and 34%, and overall survival at 9%, 53% and 79%. I think that it does help to stratify patients and it's been shown in this in a number of other trials to be helpful.

The CLL IPI trial has also been helpful in defining survival in the era of chemoimmunotherapy. Low-risk patients may have maybe a 93% progression-free survival at 5 years, intermediate risk maybe 79%, and high risk 63%, and very high risk with all the risk factors may have a 23% overall survival. And I think that the nature of how these prognostic factors are operating in the era of targeted therapy is now being researched. There is a paper that came out in June of this year in 2024 by the German CLL Study Group, and they looked at whether the CLL IPI score could actually help stratify patients in the era of targeted therapy. And I think it still does, although the distinctions between low-risk and the very-high-risk subgroups seem to be blunted in that the very-high-risk and the high-risk groups are indeed doing better.

And that's potentially true also with the CLL4 study. So I think that the advent of targeted therapy has really improved patient survival, particularly in the high-risk and very-high-risk categories; that may be lessening the distinction between that and the low-risk categories.

One thing I'd like to shout out though, is the mutation in TP53, which still appears to be an adverse criteria even in the era of targeted therapies. So I think it's important that we pay attention to this and do cytogenetics with FISH for del17p analysis, as well as to try and look at the mutation of TP53 when actually assigning the risk of poor progression or response to targeted therapies or chemoimmunotherapy.

Thank you very much. I hope that you have enjoyed this discussion.

Announcer:
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