for the first time Aiolos overexpression in primary lymphoma tissues, which could be exploited in future clinical trials.

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References


To the editor:

Eliminating the complete response penalty from myeloma response assessment

At the 2007 American Society of Hematology meeting, there were several presentations on the significant activity of combinations of novel agents with melphalan and prednisone for elderly patients with newly diagnosed myeloma. However, evaluation of the relative benefit for these different regimens is difficult given the different methods each trial used to assess progression free and event free survival. This is further complicated by the fact that several of these trials have defined progression, specifically progression from complete remission, in different ways. The frequency of complete response (CR) has dramatically increased...
over the past years, reflecting significant improvements and efficacy in our treatment options. Previously, CR required no visible band in the serum protein electrophoretic pattern, while more recently, the uniform response criteria requires not only negative immunofixation, but also a normalized free light chain ratio. These more stringent definitions are important as they define disease states with lower tumor mass, and in most studies are associated with improved duration of remission and overall survival. However, many nonlaboratory-based practitioners may not realize that immunofixation is a qualitative test and is subject to interpretation. It requires manual inspection of the immunofixation pattern to determine whether a discrete monoclonal band is visualized. This can cause variation in reported results over successive months between “absent,” “possible,” or “small monoclonal protein.” Moreover, high-dose chemotherapy or other treatment modalities that induce complete remissions are often associated with the development of posttransplantation monoclonal or oligoclonal bands that do not appear to be the same as the original M-protein, and yet can be difficult to distinguish from either relapse or normal hematopoietic recovery.

These issues regarding the accuracy of immunofixation do not impact decisions regarding therapy, as few clinicians reinitiate therapy in an asymptomatic patient with only biochemical evidence of progression. It does however cause difficulty when large groups report outcomes of trials in which there are high rates of CR. Progression from a CR requires only conversion from immunofixation negative to immunofixation positive in a single instance, while progression from any other disease response state requires an increase in the M-protein by 25% and an M-protein increase greater than 0.5 g/dL. Because the duration of response in a patient who achieves a CR is measured from the time a complete response is verified to the time the monoclonal protein reappears, it is possible to have shorter response durations among CR patients than in those patients who achieve only a partial response.

This difference in definition of progression between CR and other responses results in a distortion of the therapeutic benefit of a complete response and results in artificial reporting that reduces the value of the information for practicing clinicians. One potential way to circumvent this problem is to report response rates from these trials as an amalgamation of CR plus very good partial response (VGPR, > 90% reduction in the M-protein). Progression in the setting of a CR would then be defined as the presence of a protein level greater than a VGPR, which would by definition require that the M protein be greater than 10% of its original value. This would eliminate labeling a patient as having progressive disease based on reappearance of the band by immunofixation and would align it to the recently introduced and accepted VGPR. We would, therefore, propose that cooperative groups consider reporting CR plus VGPR as an aggregate percentage, and that the time to progression be defined as the time from the date of response to the date at which the M protein exceeds VGPR values, that is, greater than 10% of the original M protein size. Use of this approach will provide a clinically useful gauge for the durability of remission for patients who achieve a major response to therapy, and will eliminate the paradoxically shorter response duration for patients who achieve complete remissions.

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