Comment on Martinez–Lopez et al, page 329

Could CR mean cure?

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The 2 Spanish groups, Grupo Español de MM (GEM) and Programa para el Estudio de la Terapéutica en Hemopatía Maligna (PETHEMA), report on the superiority of both–event–free survival (EFS) and overall survival (OS) in patients in whom complete response (CR) status was achieved, compared with lesser response categories (near–CR [nCR], very good partial response [VGPR], partial response [PR]), in a retrospective study of 344 myeloma patients treated between 1989 and 1998.1

By a variety of analyses, the superior outcome among CR patients was not accounted for by more favorable baseline or pretransplantation features. Based on the absence of recurrence after 11 years of continued CR, Martinez–Lopez et al suggest that such patients may be cured. While fraught with the shortcomings of retrospective analyses, a much–needed assessment is provided of the impact of depth of response on long-term outcome, with a median follow–up exceeding 10 years. The observations are at variance with reports from the Intergroupe Francophone du Myelome (IFM), which found the value of VGPR over PR on EFS and OS, although immunofixation (IF)–derived CR status had not been routinely performed.2

Historically, it is important to remember that, until the introduction of high–dose melphalan therapy, < 5% of myeloma patients achieved CR. As CR increments translated into EFS and OS benefits, many strategies have since been employed toward realizing this early treatment objective, including tandem transplantations, consolidation and maintenance interventions, and, more recently, the up–front addition of novel agents, such as thalidomide and bortezomib.3 When employed as maintenance, novel agents imparted ongoing CR increments translating into extensions of EFS and OS.

The Spanish investigators acknowledge that their work does not account for genetic characteristics, an increasingly prognostic–dominating myeloma variable.4 The University of Arkansas team has reported that failure to achieve CR did not impact outcomes adversely when patients had a documented preceding smoldering course, had a GEP signature of monoclonal gammopathy of undetermined significance (MGUS), or presented with the CD2 molecular subtype.5 We also recently examined the issues of both attaining CR status and its duration on survival outcomes, applying time–dependent variables for CR onset and its sustenance as well as landmark techniques.6 Sustaining CR for at least 3 years was associated with superior outcome while patients attaining but losing CR status within 3 years had a dismal prognosis (linked in part to high–risk genomics); those failing to enter CR had an intermediate prognosis. None of the above considerations account for imaging–defined CR. In fact, several groups have reported on the prognostic consequences of MRI–defined focal lesions that resolve with a significant time delay of 18 months beyond IF–CR, attesting to the increasingly recognized heterogeneity of myeloma, which includes a nonsecretory component that contributes to late relapses often involving extramedullary sites.7,8

Even with purportedly greater cure potential provided by a graft–versus–myeloma effect of allogeneic stem cell transplantations, relapses do occasionally occur as late as 15 and 20 years after such intervention. The possibility exists that such recurrences ensue from long–dormant focal lesion sites or represent progression from other clones of a genetically heterogeneous MGUS. Such exceptions, however, cannot be used as an argument against the curability in general of myeloma, as they pertain also to childhood ALL and other malignancies with accepted cure potential.

The following should be considered in ongoing clinical investigations of myeloma therapy:

- A comprehensive genomic/genetic classification of myeloma is needed to determine whether CR implications are myeloma risk– or subtype–specific.
- Given the focal nature of bone marrow involvement of most myeloma cases, MRI and PET should become an integral part of major trials assessing the relationship of quality of response to outcomes, as imaging–defined CR may outweigh traditional myeloma protein– and bone marrow–defined CR.
- There is the possibility that the clinical consequences of CR vary not only according to myeloma genetics and risk, but are also influenced by specific treatments applied.
- While tumor cytoreduction is important for extending survival of patients with all cancers, the absence of achieving CR in myeloma should not frighten patients, as it may reflect reversal to a preceding MGUS state.

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