different diseases. These unknowns aside, the delivery of CD40L from T cells may differ from organ to organ and even within a single organ.7 Endothelial cell activation via delivery of CD40L from T cells may differ from other sources, such as platelets or microparticles. Therefore, it is important to discover the role of CD40L-bearing cells in different diseases. These unknowns aside, the door is open to tackling the new exciting targets of down-stream CD40 signaling in endothelial cells.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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Comment on Rosinol et al, page 3591

Is more better in myeloma?

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Rosinol and colleagues report the results of a Spanish PETHEMA trial in this issue of Blood. Their study was an attempt to address the role of additional intensive treatments for patients failing to achieve a complete or nearly complete remission after a single autologous transplantation.

In spite of major advances in treatment over the past decade, multiple myeloma still remains a largely incurable disease. This has led some investigators to abandon any attempt to achieve a cure and treat myeloma as if it were a chronic disease, mainly relying on the novel drugs such as bortezomib, thalidomide, and lenalidomide with or without conventional chemotherapy at low doses. Others have further increased treatment intensity by introducing a second autotransplantation or an initial autologous transplantation followed by a reduced-intensity allo-transplantation, in an attempt to obtain long-term survival or cure. Which of these different approaches is superior is still a matter of intense debate, although physicians need to remember that long-term outcome data (>7 years) are available for transplantation, but not for the newer drugs. The PETHEMA patients either received a second autograft (second autologous stem cell transplantation [ASCT]) or an allograft with a reduced-intensity conditioning regimen (allo-RIC). Because of the older age of most myeloma patients, full myeloablative allo-transplants are seldom used anymore. As is typical for such studies, a biological randomization was applied. The authors found that allo-RIC in the PETHEMA patient population resulted in a higher complete remission (CR) rate and a trend toward a longer progression-free survival. However, this procedure was associated with a higher treatment-related mortality and no benefit was observed in terms of event-free and overall survival. This again highlights the problem with allo-transplantation for myeloma. Benefit from an allo-transplant requires a graft-versus-myeloma effect, which is only seen in patients who develop graft-versus-host disease (GVHD), especially chronic GVHD. GVHD is associated with a high procedure-related mortality, which remains unacceptably high in myeloma and tends to occur later with allo-RIC. Of note, in this study the CR rate with high-dose melphalan prior to the second ASCT, now considered the gold standard, was not different than with allo-RIC. The major shortcomings of the study are the small numbers of patients included in the allo-RIC arm and the absence of information on the genetic features of patients enrolled in the study. Because genetic characterization is by far the most important prognostic factor in myeloma,1 it is difficult to assess if the groups going onto the second ACST versus the allo-RIC arm are really comparable. Even the outcome results with a second ASCT are difficult to assess because of different conditioning regimens applied to these patients. As the authors rightfully conclude, allo-transplantation in myeloma should only be performed in the context of a clinical trial because of its high treatment-related mortality. In contrast, a second ASCT has a less than 2% procedure-related mortality. Ultimately, the best results might be obtained by autotransplantation followed by maintenance therapy with the newer drugs as suggested by the Intergroupe Francophone du Myelome (IFM) study with thalidomide,2 or even better, maintenance therapy with a combination of the newer drugs as suggested by the recently published and encouraging preliminary data on Total Therapy 3.3 With the latter approach, the expectation of a median survival of more than 10 years for newly diagnosed myeloma patients has become a reality. To achieve a cure, a better understanding of the genetic makeup of the drug-resistant myeloma cells persisting after transplantation will be required, whether those drug-resistant cells represent myeloma stem cells or not.

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