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A TAD better for myeloma therapy?

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In this issue of Blood, Lokhorst and colleagues report on the results of HOVON-50, a phase 3 randomized trial designed to evaluate the effects of thalidomide during induction treatment and as maintenance in patients with multiple myeloma. There were 556 patients randomly assigned either to 3 cycles of VAD or to TAD. All patients were to receive high-dose melphalan with autologous stem cell support followed by maintenance with interferon for the VAD arm or thalidomide for the TAD arm.1 This study together with other randomized and nonrandomized trials establish a definitive role for thalidomide as induction therapy in conjunction with dexamethasone, anthracyclines, and alkylating agents.

Since the discovery of its activity against multiple myeloma, the role of thalidomide in the treatment of myeloma has been extensively explored.2 The HOVON-50 study represents the latest of these large, randomized trials whose primary objective is to define the role of thalidomide as induction and maintenance therapy for myeloma. The addition of thalidomide to the combination of an anthracycline and steroids was associated with a significantly improved overall response rates prior to high-dose therapy (71% vs 57%), including a significantly higher rate of very good partial response (90% or more reduction in tumor burden) of 37% versus 18% for the vincristine, doxorubicin, and dexamethasone (VAD) arm. However, the relevance of these findings in the context of newer induction therapies combining the proteasome inhibitor bortezomib, an immunomodulatory drug (IMID; such as thalidomide or lenalidomide), and steroids remains to be determined.3-6

This point is illustrated in the table, which compares the response rates of standard thalidomide-containing induction regimens with more modern bortezomib–IMID combinations. Thus, traditional thalidomide–based induction either with steroids alone or in combination with an anthracycline or an alkylator may be better than nonthalidomide–based inductions. The results may be inferior to what can now be obtained with IMID–bortezomib combinations.

Underscoring this point are the results of the most recent GIMENA trial presented by Cavo et al at the American Society of Hematology meeting in San Francisco. In the study, 450 patients with newly diagnosed myeloma were randomized to receive thalidomide in combination with dexamethasone either with or without bortezomib. Patients randomized to the bortezomib arm had a significantly higher response rate and complete response rate than those who did not receive bortezomib. More importantly, progression-free survival at 2 years was 90%, significantly better than the 80% seen in the thalidomide dexamethasone arm, with as yet no significant impact on overall survival at 2 years (96% vs 91%).3

The HOVON-50 trial confirms the beneficial role of thalidomide as maintenance therapy after autologous stem cell transplantation with an improvement in median progression-free survival from 22 months to 34 months. No survival benefit for thalidomide maintenance was seen due to the shortened survival after relapse seen in the thalidomide dexamethasone arm, but only 50% of patients received salvage bortezomib and less than 20% received lenalidomide therapy.

In summary, the results of HOVON-50 strongly support the use of thalidomide as induction and maintenance therapy in patients with myeloma. However, in the context of emerging data from ongoing trials using bortezomib and lenalidomide combinations, the tad improvement obtained with thalidomide, doxorubicin, and dexamethasone (TAD) may just not be the best that can be obtained with current therapy. Large, randomized trials are currently ongoing to address this and other clinically relevant questions in myeloma therapy today. We should all continue to support them.

Conflict-of-interest disclosure: S.G. is on the speakers bureau of Celgene, Novartis, Millennium, and Genzyme.
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In this issue of Blood, Fauriat and colleagues find that the expression of KIR2DS1 by human NK cells is associated with a decreased responsiveness to various stimuli in HLA C2/C2 but not in C1/C1 persons. How natural killer (NK)—cell responsiveness is controlled is an unresolved and fascinating question. A major breakthrough in this field of investigations was made when NK cells expressing inhibitory KIR (human) or Ly49 (mouse) capable of interacting with endogenously expressed major histocompatibility complex (MHC) molecules were found to be hyperresponsive to stimulation through various receptors. This counterintuitive result led to the concept of “licensing” or “education,” a process by which a chronic interaction of inhibitory KIR or Ly49 with their MHC ligands would promote NK-cell responsiveness through unknown mechanisms. Recent data in mouse models suggested that activating receptors also participate in this educational process but in the opposite direction. Indeed, it was found that overexpression of ligands for an activating Ly49 or for NKG2D led to a decreased responsiveness of NK cells. In this issue of Blood, Fauriat et al investigate the consequences of KIR2DS1 expression on NK-cell responsiveness. KIR2DS1 is an activating KIR known to interact with HLA-C molecules of the group 2 but not to those of the group 1. They took advantage of a combination of anti-KIR antibodies to track KIR2DS1 positive NK cells in human peripheral blood mononuclear cells. Next, they set up a 9-color flow cytometry procedure to track every combination of KIR and NKG2A/CD94 molecule expression on NK cells and assess their responsiveness to various stimuli. Of note, this flow cytometry procedure is certainly powerful but potentially limited by steric hindrance of epitopes, considering that 7 antibodies coupled to sometimes very big fluorochromes are used to stain the same cells. Despite this potential technical limitation, data by Fauriat et al clearly indicate that KIR2DS1 influenced NK—cell responsiveness in donors of the C2 group but not in donors of the C1 group. More precisely, they found that KIR2DS1 simple positive NK cells are hyporesponsive to stimulation through various receptors in comparison with KIR-negative NK cells. Moreover, they found that expression of KIR2DS1 by NKG2A-positive NK cells decreases their responsiveness (see figure). These results provide the first evidence that the interaction of an activating KIR with its cognate ligand may modulate NK-cell responsiveness in a physiological setting.

As discussed by the authors, these results fit well with the “rheostat” model of NK—cell responsiveness. This model proposes that NK—cell responsiveness varies in a wide range, regulated by the level of expression of MHC molecules and the number of inhibitory receptors capable of interacting with these molecules. They propose that activating KIR would be another parameter of this equation, working against responsiveness. However, several issues remain to be addressed. In particular, when, where, and under which conditions does education occur? How do NK cells integrate the various educating stimuli? And perhaps most importantly, how can the same ligand/receptor pair (eg, KIR-L/MHC) increase NK—cell responsiveness in an educating context and inhibit NK—cell activation upon interaction with a target cell? Exploration of signaling complexes downstream activating and inhibitory receptors in educating or triggering conditions may provide clues to understand this complex phenomenon.

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