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An ounce of which prevention is worth a…?

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In this issue of *Blood*, a randomized clinical trial reported by Kennedy et al[1] showed that adding the monoclonal interleukin-6 (IL-6) receptor antibody tocilizumab to standard graft-versus-host disease (GVHD) prophylaxis had only a modest effect on the incidence of acute GVHD (aGVHD).

In the study, patients with acute myeloid leukemia or myelodysplastic syndrome undergoing sibling or unrelated donor allogeneic hematopoietic cell transplantation (HCT) received a single dose of tocilizumab or placebo on day −1. GVHD prophylaxis was by cyclosporine and short-course methotrexate. The goal was to prevent grade 2-4 GVHD. With 145 patients randomized, tocilizumab was associated with a somewhat lower incidence of aGVHD (27% vs 36%), but the difference was not statistically significant. The difference was seen mainly in grade 2 aGVHD and not at higher grades. There was no difference in nonrelapse mortality (NRM).

This is a negative study. The investigators are to be commended for running an investigator-initiated placebo-controlled double-blind randomized clinical trial attempting to provide an answer to a specific question. As is often the case, answers are partial, and new questions arise: would a larger N make the difference significant? Is there a difference in chronic GVHD (cGVHD; not fully reported in the article) that could impact quality of life? Is a single dose on day −1 the best way to use this antibody? In 2 previous phase 2 studies, the incidence of aGVHD had been lower than expected, after adding tocilizumab to standard GVHD prophylaxis.[2,3] Unfortunately, it is common for treatment effect differences in randomized clinical trials to be smaller (9% vs 28%) compared to preceding phase 2 studies. These often describe results of the experimental treatment in comparison to standard treatment, with the standard treatment group drawn from observational historical patient cohorts.

GVHD prophylaxis is a double-edged sword, a balancing act between cure of disease through the graft-versus-leukemia effect and harm by GVHD, with T cells being the ultimate key player for both. Donor T-cell activation and effector differentiation are the final steps of a cascade starting with inflammation because of tissue damage, as shown in murine models. IL-6 is a key regulator in this cytokine network.

The main outcome measure of effective GVHD prophylaxis is reducing aGVHD incidence, as well as preventing aGVHD and cGVHD without increasing the risk of malignancy relapse and infections.[4] Therefore, studies need to be evaluated for the incidence of acute and chronic GVHD, relapse incidence, leukemia-free survival, and the compound outcome of GVHD-free (severe aGVHD and cGVHD requiring treatment) and relapse-free survival (GRFS).[5] This risk differs in nonmalignant disease, where relapse is not a concern. GVHD risks depend on the GVHD prophylaxis used, on donor type (lower with HLA-identical siblings, higher with unrelated and HLA-mismatched related donors), on stem cell source (marrow or peripheral blood), and on the intensity of the conditioning regimen causing tissue damage, which modulates GVHD risks.

Calcineurin inhibitors, added to methotrexate used in the 1980s, became standard and made allogeneic HCT possible.[6] Extensive in vitro T-cell depletion was introduced and mostly abandoned because of increased graft failure and relapse risks.[7] Several randomized controlled trials tested in vivo T-cell depletion using polyclonal anti-thymocyte globulins (ATGs); these effectively reduce GVHD risks, cGVHD more than aGVHD, but they also increase relapse incidence and infectious complications to some degree. The net effect differs across trials, probably based on the inherent relapse risk in the population studied.[8,9] Use of ATGs is common, mainly in unrelated donor HCT, based on the perception of better quality of life, given the lower incidence of cGVHD even without decreased NRM. More recently, ablation of alloreactive lymphocytes early after HCT with high doses of cyclophosphamide given on days 3 and 4 after transplantation was pioneered for haploidentical HCT and has been found useful for other situations.[10] New avenues explore mTOR inhibitors, JAK1/2 inhibitors, different approaches to cytokine and costimulation blockade, and pathways such as ROCK2.

It is too early to abandon tocilizumab. The pathophysiology of GVHD is complex; it is unlikely that blocking a single pathway will provide the answer. Possibly combined interventions in cellular and cytokine networks will be more successful. Studies require planning, such that a 10% decrease in the incidence of aGVHD is significant. Even if small, such a difference can be clinically relevant. Progress in medicine is often through multiple small steps rather than giant leaps. This measured effect has to affect downstream events favorably (ie, decrease NRM without increasing relapse risks). GRFS is an attractive outcome measure and is likely to provide significant results in statistical comparisons, because the number of events is higher in compound outcome measures compared with its single components. GRFS provides a numerical assessment of transplant success and is useful as a proxy of health status after HCT. However, it is the impact on the different components of GRFS that will be convincing to change drug treatment practice for GVHD prophylaxis. Therefore, we need large trials with sufficient power to dissect differences in GVHD incidence resulting in decreased NRM without increasing relapse.

Conflict-of-interest disclosure: The authors declare no competing financial interests ■

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