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Bortezomib for prevention of acute graft-*versus*-host disease: a conclusion reached

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Prevention of acute graft-*versus*-host disease (GvHD) after allogeneic hematopoietic cell transplantation (HCT) has long posed a major challenge for the field. In this issue, Koreth *et al.*[1] report results of a randomized three-arm phase II trial testing two different immunosuppressive regimens using bortezomib to prevent acute GvHD after allogenic hematopoietic cell transplantation. Contrary to expectations, the results did not show major improvement in the experimental groups as compared to the control group.

The impetus to explore the use of bortezomib to prevent GvHD came from its mechanism of action to prevent signaling through nuclear factor (NF)κB in activated T cells. In resting T cells, the inhibitor (I)-κB binds to NFκB as a complex that is sequestered in the cytoplasm.[2] In activated T cells, ubiquitin moieties attach to I-κB, which is delivered to proteasomes. The NFκB molecules released from I-κB translocate to the nucleus where they activate the transcription of genes involved in immune responses. Among other possible mechanisms of action, bortezomib inhibits proteasome activity, allowing I-κB to prevent NFκB-mediated activation of T cells.

Experimental results showed that administration of bortezomib early after allogeneic HCT could prevent acute GvHD in mice.[1] These results led to a phase I/II study demonstrating that bortezomib can be combined with tacrolimus and methotrexate in a tolerable post-transplant immunosuppressive regimen after HCT with human leukocyte antigen (HLA)-mismatched donors. Results of the completed study were published in 2012[3] and are summarized in Figure 1. The interpretation of the 2012 study was initially informed by historical experience showing a 46% incidence of grade II – IV GvHD in patients with HLA-mismatched unrelated donors.[4] The 22% incidence of grade II – IV GvHD in the 2012 study was indeed encouraging when compared against this benchmark, although the comparability of demographic and treatment characteristics of patients in the phase I/II study and the historical group[5] was not well documented.

In the current study of HLA-matched unrelated HCT, the benchmark for grade II – IV GvHD was set at 40%.[1] The observed 33% incidence of grade II – IV GvHD in patients treated with tacrolimus and methotrexate (Arm A) was somewhat lower than this benchmark, while the 29% incidence in patients treated with bortezomib added to tacrolimus and methotrexate (Arm B) was somewhat higher than the 22% incidence observed in HLA-mismatched recipients in the phase I/II study (Figure 1). As a result, the current study did not demonstrate a statistically significant improvement following the addition of bortezomib to tacrolimus and methotrexate in patients with HLA-matched unrelated donors.

Results of the current study with HLA-matched unrelated recipients are similar to those observed in the BMT CTN 1203 PROGRESS study, which enrolled a mixed cohort of HLA-matched related and unrelated recipients and a small proportion of HLA-mismatched unrelated recipients. In this study, the day 180 cumulative inci-

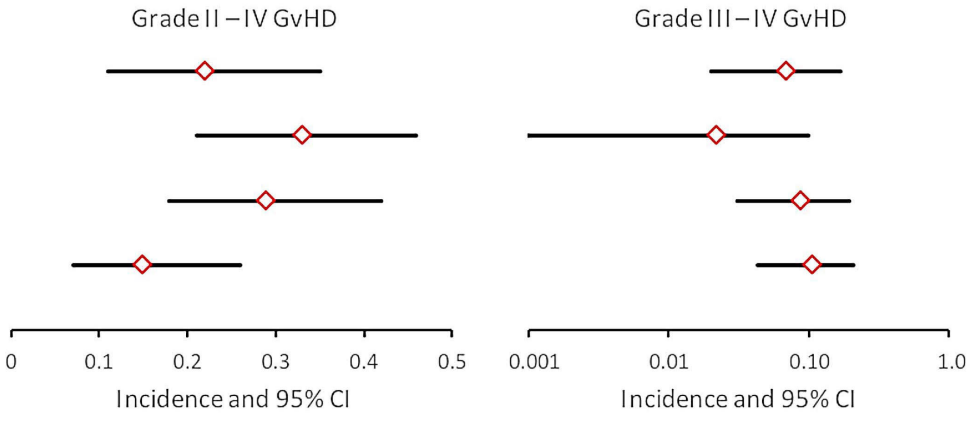

Figure 1. Summary of key results from Koreth *et al.*[3] (JCO 2012) and from the current study.[1] Results are shown for Arm A (tacrolimus and methotrexate), Arm B (bortezomib added to tacrolimus and methotrexate) and Arm C (bortezomib and tacrolimus with sirolimus substituted for methotrexate), as compared to tacrolimus and methotrexate used in the JCO 2012 study.[3] Diamonds indicate the incidence frequencies of grades II – IV GvHD and III – IV GvHD, and bars indicate the 95% confidence intervals. All patients in the JCO 2012 study had HLA-mismatched unrelated donors. In Arms A, B and C of the current study, all patients had HLA-A, B, C, DRB1–matched unrelated donors. Data in the figure exclude GvHD that occurred after relapse of the pretransplant disease. Results for grade III – IV GvHD are shown on a log scale in order to visualize the lower limits of the 95% confidence intervals more clearly. GvHD: graft-*versus*-host disease; CI: confidence interval.

dence frequencies of grade II – IV GvHD were 31% in control patients treated with tacrolimus and methotrexate, and 26% in patients treated with bortezomib added to tacrolimus and methotrexate.[6]

Arm C of the current study[1] tested a regimen of bortezomib and tacrolimus with the substitution of sirolimus for methotrexate when compared to Arm B. This substitution was motivated by a desire to enhance the survival and function of T-regulatory cells, thereby possibly facilitating the development of tolerance. The 15% incidence of grade II – IV GvHD in this group appears to be encouraging when compared against the 33% incidence in Arm A. More importantly, however, the results for grade III – IV GvHD were somewhat higher in Arms B and C than in Arm A. Here, the 9% incidence in Arm B and the 11% incidence in Arm C appear to be consistent with the ~10% incidence of grade III – IV GvHD observed with other current approaches, while the 2% incidence in Arm A appears to be much better than expected. In the BMT CTN 1203 PROGRESS study, for example, the cumulative incidence frequencies of grades III – IV GvHD were 13% in the controls treated with tacrolimus and methotrexate, and 8% in patients treated with bortezomib added to tacrolimus and methotrexate.[6]

The current results raise the question of whether data from the phase I/II trial truly justified the effort to investigate bortezomib-based immunosuppression in the subsequent three-arm trial and the BMT CTN 1203 PROGRESS trial. Enthusiasm for these studies was based primarily on a comparison of outcomes between patients enrolled in the phase I/II study and a group of 176 patients who received tacrolimus and sirolimus for immunosuppression after HLA-matched unrelated transplantation.[3] In this comparison, the 22% incidence of grade II – IV GvHD in the phase I/II study did not differ statistically from the 11% incidence in the 176 patients with HLA-matched unrelated donors. The absence of statistical significance therein, however, cannot be interpreted as indicating that the incidence rates are similar. *P*-values >0.05 indicate only that the results were not demonstrably different between the two groups, given their respective sizes. In this case, the comparison actually showed a two-fold difference in the incidence of grade II – IV acute GvHD.

A further question is whether grade II – IV GvHD actually represents the most appropriate primary endpoint in studies evaluating immunosuppressive regimens after allogeneic HCT. Results of a recent CIBMTR study showed that grade II acute GvHD has no statistically significant association with the risk of treatment failure defined as death or relapse, whereas grades III and IV acute GvHD were associated with increased risks of treatment failure.[7] These observations suggest that clinical trials should focus on preventing grade III – IV acute GvHD, as opposed to grade II – IV acute GvHD. The prior report by Koreth *et al.*[3] did not compare the incidence rates of grade III – IV acute GvHD between patients enrolled in the phase I/II study and the 176 patients who received tacrolimus and sirolimus for immunosuppression after HLA-matched unrelated transplantation.

To some extent, we have become victims of our own success in our efforts to prevent grade III – IV acute GvHD. A 1:1 randomized trial would require approximately 200 patients per arm to test the difference between a 10% incidence and a 3% incidence at 80% power and a 0.05 two-side type-1 error. A larger effect size would require fewer patients. As an alternative, survival to 1 year without prior grade III – IV acute GvHD, chronic GvHD requiring systemic treatment, or relapse has become a very popular compound endpoint for acute GvHD prevention studies.[7] Current typical estimates for this GvHD-free/relapse-free survival (GRFS) endpoint are in the 35% range, which leaves considerable room for improvement.[7] However, grade III – IV acute GvHD makes the smallest contribution among the four components of this compound endpoint. Moreover, the risks of non-relapse mortality and relapse are heavily influenced by factors that are not associated with the risk of grade III

– IV acute GvHD. For these reasons, the GRFS endpoint represents an unreliable surrogate for the ability of an intervention to prevent grade III – IV acute GvHD.

The current report by Koreth *et al.*[1] represents a well-controlled attempt to evaluate the merits of bortezomib for immunosuppression after HCT with reduced intensity conditioning regimens. The report is newsworthy, because the negative results do not support expectations that bortezomib-based regimens might have a major effect on the risk of grade III – IV acute GvHD, even with the substitution of sirolimus for methotrexate in Arm C. With the benefit of hindsight, one could question whether the expectations based on results of the phase I/II study were realistic.

The experience from testing bortezomib yields important lessons for planning future trials. First, grade III – IV acute GvHD should be defined as the primary endpoint in trials designed to test an intervention intended to prevent acute GvHD. Second, the benchmark incidence of grade III – IV acute GvHD should be set at 10 – 15%, depending on the relationship and HLA-matching between the donor and recipient. Third, early phase trials should be designed to test whether an intervention can reduce the incidence of grade III – IV acute GvHD to 2% or less, as it will not be feasible to determine whether any smaller effect size holds true in a phase III trial. Early phase and later phase trials should have rules that discontinue enrollment when initial results indicate that the intervention is not likely to reach this benchmark of success. Finally, although the GRFS endpoint should not be used as the primary endpoint in trials of interventions intended to prevent grade III – IV acute GvHD, it remains important to demonstrate that successful prevention of grade III – IV acute GvHD does not come at the expense of increasing the risk of non-relapse mortality or the risk of recurrent or progressive malignancy.

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Use of desmopressin in the treatment of hemophilia A: towards a golden jubilee

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Throughout the 1970s, the availability and safety of coagulation factors, employed for replacement therapy in patients with hemophilia (PWH), were very far from what they are nowadays. Plasma-derived concentrates of factor VIII (FVIII) and IX started to be industrially manufactured, but they were generally available in limited amounts in most countries, and thus used only for the acute treatment of bleeding episodes (so called 'on-demand regimen'), but not for the treatment of choice, i.e., the prevention of bleeds by means of regularly spaced infusions (prophylaxis regimen). Most importantly, these products, produced from plasma pooled from thousand of donors, transmitted the hepatitis viruses with extremely high frequency; the agent causing hepatitis B and, more often, the so called non-A, non-B virus, which was only identified in 1989 as the hepatitis C virus. These bloodborne viruses heralded the bleak era of infection with the human immunodeficiency virus (HIV), that started to contaminate plasma-derived coagulation factor concentrates at the end of the 1970s, eventually leading to the first appearance in PWH of the acquired immunodeficiency syndrome (AIDS) in 1982, which caused such a high toll of deaths during the 1980s and the 1990s.

With this background, it is not surprising that in the 1970s and earlier a multitude of research efforts were directed towards the development of pharmacological alternatives to blood products. These agents were felt particularly necessary in patients with mild hemophilia A who, having measurable plasma levels of FVIII of 6% of normal or more, bleed much less frequently than those with severe disease and unmeasurable FVIII levels. In general they have little risk of mortality and morbidity, and their main clinical problem is excessive bleeding after trauma or surgery whereas, at variance with severe hemophilia, spontaneous bleeding episodes and joint