not activate complement, showed low levels of platelet activation, did not cause fibrinogen activation as did other polybasic compounds, and had antithrombotic activity in 2 mouse models of arterial thrombosis causing less bleeding than heparin.1 Surprisingly, the best polyP inhibitor in vitro (UHRA 8) did not perform as well as others tested in vivo, and the authors cannot conclusively rule out that polyP binding is the only basis for their ability to inhibit thrombus formation in vivo.1

Interestingly, the mode of action of these compounds differs from that of conventional antithrombotics. Because long-chain polyP is more effective in triggering the contact pathway of blood coagulation and is abundant in microbes, a potential clinical use of these compounds in sepsis and disseminated intravascular coagulation is envisaged.1 Overall, this study dramatically changes our insights regarding the role of polyP in thrombosis and sets the stage for the pursuit of new clinically useful compounds.

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

REFERENCES


© 2014 by The American Society of Hematology

Clinical Trials & Observations

Comment on Bolaños-Meade et al, page 3221

The end of knight-errantry in GVHD studies

Marcos de Lima

In this issue of Blood, Bolaños-Meade et al reported the results of the randomized phase 3 study Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0802.1 It compared the addition of mycophenolate mofetil to steroids vs steroids/placebo to treat newly diagnosed acute graft-versus-host disease (GVHD). Unfortunately, it failed to show a significant difference in outcomes.

In writing this commentary, I could not avoid the temptation to make a literary analogy. That brings me to Alonso Quixano, aka Don Quixote, a complex character that, according to one of the possible interpretations of Miguel de Cervantes’ masterpiece, reflects the end of chivalry, a man who represented the transition of times. In his highly unorthodox ways, Quixote seemed to get more and more “rational” toward the end of the book. Cervantes, as an author, made the leap from chivalric romance to modern literature.2 I believe we are witnessing a similarly important transition in our field of hematopoietic stem cell transplantation.

Steroids remain the standard of care for the treatment of GVHD. This statement has held true since the 1970s, and GVHD remains a major cause of treatment failure for recipients of allogeneic transplants. The paucity of randomized, multicenter studies in this field reflects both the complexities of the problem and the lack of a collaborative instrument to mediate and coordinate such efforts in the United States. The latter changed dramatically with the creation of the BMT CTN. As a matter of fact, the study reported here stems from a previous prospective randomized phase 2 study (BMT CTN 0302) that evaluated GVHD response rates to pentostatin, mycophenolate mofetil, denileukin difitox, or etanercept added to steroids for the first-line treatment of acute GVHD. The best outcomes were observed with mycophenolate, and included a day 56 GVHD-free survival of 71%.3 Although somewhat frustrating in that the hypothesis that led to the phase 3 trial turned out to be refuted, the logical sequence of questions posed here point to the inability of underpowered studies (usually performed by single institutions) to replace larger randomized studies (ideally multicenter), and also reinforce the need to support the infrastructure that makes such studies possible.

The benefit to our patients is clear. In the big scheme of disease prevalence, hematologic malignancies (the main indication for allogeneic transplantation) are a relatively small fraction of the universe of conditions that need treatment improvement. GVHD occurs in a fraction of those patients, and due to the small numbers, attracts less attention from the public and medical community at large (although it certainly does not feel like an orphan disease to our patients and to hospital staff who take care of them). Therefore, in order to answer critical questions and to achieve strength in numbers, cooperative efforts are needed. The role of the National Heart, Lung, and Blood Institute (NHLBI) in supporting the BMT CTN enterprise cannot be overemphasized.

As for the trial itself, the mycophenolate arm had more advanced disease patients than the placebo group, likely explaining the decreased disease-free survival in the former subgroup (10% inferior, although this did not reach statistical significance). BMT CTN 0802 conclusions do not necessarily apply to “alternative” donor cord blood or haploidentical transplants, or to pediatric patients, given the underrepresentation of these patients in the population studied here. It is interesting to know that day 56 GVHD-free survival, the primary endpoint for 0802, was...
59.5% vs 50.4% for the controls. This should be compared with 47% on the nonmycophenolate arms of the preceding study 0302, which provided the lower boundary for estimating efficacy in this randomized comparison. Ultimately, the trial was stopped early because the futility rules were triggered after the first planned interim analysis.

Where do we go from here? Could high-risk patients be identified early using biomarkers, and referred for GVHD combination approaches, as suggested by Bolaños-Meade et al? Roughly 70% of the patients enrolled in this trial had grade 1 or 2 acute GVHD, a group which historically has the highest response rates to standard therapy. It remains unknown whether the combination of mycophenolate and steroids would have proven superior had higher risk patients been targeted for this trial. Risk stratification of patients with newly diagnosed acute GVHD will form the cornerstone of acute GVHD studies in the next decade, wherein patients who are likely to fail with standard therapy are enrolled onto trials with novel and often organ-specific agents, whereas patients with favorable prognostic covariates are targeted for steroid-sparing strategies. It is quite frustrating that although steroids remain the backbone of GVHD treatment, ~35% to 50% of patients will have some degree of steroid refractoriness, with very poor outcomes. Undoubtedly, testing of novel GVHD prevention strategies with trial endpoints targeting not only a reduction in severe grade 3/4 acute GVHD but also chronic GVHD rates is needed. To this end, BMT CTN 1203 is set, this month, to open a prospective phase 2 evaluation of 3 novel agents, whereas patients with favorable prognostic covariates are targeted for steroid-sparing strategies. It is quite frustrating that although steroids remain the backbone of GVHD treatment, ~35% to 50% of patients will have some degree of steroid refractoriness, with very poor outcomes. Undoubtedly, testing of novel GVHD prevention strategies with trial endpoints targeting not only a reduction in severe grade 3/4 acute GVHD but also chronic GVHD rates is needed. To this end, BMT CTN 1203 is set, this month, to open a prospective phase 2 evaluation of 3 novel agents, whereas patients with favorable prognostic covariates are targeted for steroid-sparing strategies.

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

REFERENCES


2. de Gervantes Saavedra M. El Ingenioso Hidalgo Don Quijote de La Mancha. Spain: Ediciones Carena/Acacial; 2009.


© 2014 by The American Society of Hematology

Not merely quiescent: telomeres in quiescent HSCs

Ayako Nakamura-Ishizu1,2 and Toshio Suda1,2
1NATIONAL UNIVERSITY OF SINGAPORE; 2KEIO UNIVERSITY

In this issue of Blood, Wang et al elegantly show that telomere shortening results in DNA damage that induces apoptosis and senescence in quiescent hematopoietic stem cells (HSCs). Altering the cell cycle and retaining a quiescent state protect cells from cell-intrinsic functional exhaustion and naturally produce extrinsic cellular insults. HSCs are thus maintained in cell cycle quiescence, enabling lifelong hematopoietic cell production. However, quiescence does not ensure that HSCs will be immortal. Organismal aging is reflected on the cellular level as stem cell potentials of HSCs decline with age. The mechanisms of how aged HSCs are functionally defective have recently started to be uncovered. HSCs exhibit accumulation of DNA damage induced by intrinsic and extrinsic hazards. Initially, it was postulated that acquisition of quiescence protected HSCs from genomic instability. Yet, recent studies indicate decreased expression of DNA damage repair pathway–associated genes in quiescent HSCs compared with cycling HSCs. Attenuation of the DNA damage repair pathway leads to the accumulation of DNA damage in aged quiescent HSCs, and such damage is repaired upon cycling. Aged quiescent HSCs display a slower rate to enter the cell cycle to proliferate and display a persistent replication stress postcycling. Mechanisms underlying HSC aging are thus linked to cell cycle status and cell cycle machinery. However, a quiescent state does not necessarily ensure protection from cellular insults and genetic instability. Telomeres cap the ends of linear chromosomes, protecting chromosomes from degradation or fusion. Telomeres shorten with cell division and aging but are repaired by telomerase ribonucleoprotein complex and the shelterin complex. Telomerase is expressed in HSCs, and telomerase activity is essential for the maintenance of HSC potentials. Yet details of the mechanism underlying the effect are largely unknown. Wang et al profiled the gene expressions.

© 2014 by The American Society of Hematology
The end of knight-errantry in GVHD studies

Marcos de Lima