The Bottom Line

Intravenous versus Oral Busulfan-Based Conditioning for Pediatric Allogeneic Hematopoietic Cell Transplantations: Did The Pendulum Swing Too Far, Too Fast?

Christopher Bredeson

The Ottawa Hospital Blood and Marrow Transplant Program and Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

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Oral busulfan is an alkylating agent that provides good antileukemic activity and excellent CNS penetration. It was first introduced over 30 years ago by George Santos as an alternative to total body irradiation (TBI) for pre-allogeneic transplantation conditioning [1]. Since its introduction, it has had a mixed reputation. Oral busulfan (PO BU) proved an attractive alternative to TBI based on general availability, ease of administration, and low cost. Although the results of early randomized controlled trials were mixed, in some settings, such as sibling donor allogeneic bone marrow transplantations for chronic myeloid leukemia, PO BU- and TBI-based conditioning regimen transplantations resulted in similar outcomes [2]. Since the mid-1990s, PO BU has been 1 of the main conditioning agents for allogeneic transplantation.

Despite this, PO BU has always carried with it the shadow of significant intra- and inter-patient variability in absorption and first pass metabolism that contributes to a risk of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) that can result in significant morbidity and death in some patients. To address these metabolic limitations, an intravenous formulation of the drug was developed and approved for use in allogeneic transplantation in 1999. Compared to PO BU, the intravenous formulation of busulfan (IV BU) resulted in less patient-to-patient variability in metabolism, drug exposure, and early toxicities [3]. Early reports suggested that compared with PO BU, IV BU resulted in lower early toxicities, such as VOD/SOS, and decreased treatment-related mortality [4-6]. IV BU use has steadily increased at the expense of both PO BU and TBI. Novel dosing regimens, particularly once a day, became another attractive feature of IV BU. Although more expensive to purchase, the perceived advantages and convenience with IV BU has led many programs to switch from PO to IV BU.

With experience, however, we learned that it was not as simple as we had hoped. There remains patient-to-patient variability in metabolism and this is marked in pediatrics. The hope for a simple weight-based dose, as originally introduced, has not been borne out by practice. Therapeutic drug monitoring (TDM) based on the pharmacokinetics of the first therapeutic dose or test dose has led to a better understanding of therapeutic range for busulfan (AUC 900 to 1500 micromole x min), above which the risk of toxicity, particularly VOD/SOS, increases [7,8]. At the other end, low doses have been associated with relapse or graft failure, albeit primarily in children [9]. In a recent Center for International Blood and Marrow Transplant Research study of IV BU, 58% of adult patients receiving ablative IV BU-based conditioning had TDM performed [10]. TDM is close to universal in the pediatric setting because of the more marked variability based on size and changing metabolism with age.

Recently, there has even been a flurry of publications that have revisited the BU versus TBI debate based largely on the phase 2 data and experience with IV BU and anticipation that, perhaps now, BU would result in similar or perhaps better outcomes than TBI. This has largely been confirmed in prospective and retrospective cohort studies from the Center for International Blood and Marrow Transplant Research and European Group for Blood and Marrow Transplantation [10,11]. Still the migration to IV BU has not been complete and very good transplantation results when PO BU is combined with TDM (ie, targeted busulfan) have been reported [12]. Results appear equivalent to those achieved with IV BU.

This is the question addressed by Kato et al. in this issue of Biology of Blood and Marrow Transplantation: Are results with PO BU similar to those with IV BU [13]? Their interest in pediatric patients as previously reported data in that setting is quite limited. To address the question, they analyzed data on 460 children receiving a myeloablative conditioning allogeneic transplantation using either PO BU or IV BU and reported to the Japanese Society for Hematopoietic Cell Transplantation Registry between 2000 and 2010. Sixty percent of the children were between 1 and 10 years of age and underwent transplantation for either acute myelogenous leukemia or acute lymphoblastic leukemia, primarily in complete remission. Approximately 40% of donors were related, 43% cord, and the remainder were volunteer unrelated or unknown. A quarter had received a prior transplantation. Of note, very few patients received IV BU prior to 2004 and very few received PO BU after 2007. Essentially, this is a study of before and after introduction of IV BU in Japan. There were no significant differences in 3-year survival, nonrelapse mortality, relapse or the incidence of grades II to IV acute graft-versus-host disease for patients receiving...
PO or IV BU, whether looking at the whole population or acute myelogenous leukemia or acute lymphoblastic leukemia separately. VOD/SOS incidences with IV BU and PO BU were 30.3% and 27.4%, respectively ($P = .74$). In multivariate analysis, route of BU dosing (IV versus PO) was not associated with the outcomes of interest. Essentially, no meaningful differences in the results with IV BU versus PO BU were found: IV BU did not improve outcomes in this pediatric population.

There are, unfortunately, several key pieces of data that are not reported but are essential if one is to consider changing practice based on this report. The most critical gap is whether any, some, or all patients had TDM and BU dose adjustments. In many reports, TDM with BU is reported as essential in pediatrics. Without knowing what was done with regards to TDM and dose adjustments, the results of this study cannot be extrapolated to other centers. Also of importance are data regarding dose and schedule of the BU administration. We would also like to know how many centers contributed patients and whether all patients who underwent transplantation are reported to the Japanese Society for Hematopoietic Cell Transplantation Registry or whether it is voluntary. Registry-based research is a tricky business and to prevent unwarranted criticism, it is vital that critical details regarding the structure and processes of the registry be included in the methods. Somewhat different than what has occurred in many registry studies evaluating different therapeutic strategies, patient selection for IV versus PO BU in this report is primarily a function of time; more recent patients received IV BU and earlier patients PO. Bias in treatment assignment is likely less in this report than in many other registry studies. Similarly, because the IV BU patients underwent transplantation more recently, any advantage afforded by improvements in supportive care would favor the IV group, strengthening the argument that IV BU has itself not resulted in improvement in outcomes.

How, then, to interpret this study? If we acknowledge the limitations of the study report and accept the results that IV and PO BU resulted in similar outcomes in this pediatric population, does this mean we should abandon IV BU and go back to PO? No, I don’t think that is the take-home message. Instead, each center has to consider all the local variables and practice drivers that would favor using 1 form of BU over the other. For our adult program, the local advantages of IV BU including once a day administration, decreased nursing and pharmacy time, patient preference, and less need for TDM (although that is still a topic of much debate) mean that we are staying with IV BU. For other centers that have not switched to IV BU, I think these data are reassuring that they are not doing something wrong or short changing their patients.

The most important thing about the mechanics of transplantation is to do a limited number of things, understand what you do, and do them well. This applies equally to BU and conditioning regimens, whether IV or PO. Determine best practices for your local circumstances, continuously evaluate your outcomes, and be willing to consider new approaches that report improved outcomes supported by quality data.

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