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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 preallogeneic 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 × 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

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* Correspondence and reprint requests: Dr. Christopher Bredeson, The Ottawa Hospital, 501 Smythe Road, Ottawa, Ontario, Canada K1H8L6.
E-mail address: cbredeson@ohri.ca

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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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REFERENCES

1. Santos GW, Tutschka PJ, Brookmeyer R, et al. Marrow transplantation for acute nonlymphocytic leukemia treatment after busulfan and cyclophosphamide. *N Engl J Med*. 1983;309:1347-1353.
2. Clift RA, Buckner CD, Thomas ED, et al. Marrow transplantation for chronic myeloid leukemia: a randomized study comparing cyclophosphamide and total body irradiation with busulfan and cyclophosphamide. *Blood*. 1994;84:2036-2043.
3. Andersson BS, Madden T, Tran HT, et al. Acute safety and pharmacokinetics of intravenous busulfan when used with oral busulfan and cyclophosphamide as pretransplantation conditioning therapy: a phase I study. *Biol Blood Marrow Transplant*. 2000;6:548-554.
4. Andersson BS, Kashyap A, Gian V, et al. Conditioning therapy with intravenous busulfan and cyclophosphamide (IV BuCy2) for hematologic malignancies prior to allogeneic stem cell transplantation: A phase II study. *Biol Blood Marrow Transplant*. 2002;8:145.
5. Thall PF, Champlin RE, Andersson BS. Comparison of 100-day mortality rates associated with i.v. busulfan and cyclophosphamide vs. other preparative regimens in allogeneic bone marrow transplantation for chronic myelogenous leukemia: Bayesian sensitivity analyses of confounded treatment and center effects. *Bone Marrow Transplant*. 2002;33:1191-1199.
6. Kashyap A, Wingard J, Cagnoni P, et al. Intravenous versus oral Busulfan as part of a busulfan/cyclophosphamide preparative regimen for allogeneic hematopoietic stem cell transplantation: decreased incidence of hepatic veno-occlusive disease (HVOD), HVOD related mortality and overall 100-day mortality. *Biol Blood Marrow Transplant*. 2002;8:493.
7. Slattery JT, Sanders JE, Buckner CD, et al. Graft-rejection and toxicity following bone marrow transplantation in relation to busulfan pharmacokinetics. *Bone Marrow Transplant*. 1995;16:31-42.
8. Geddes M, Kangarloo SB, Naveed F, et al. High busulfan exposure is associated with worse outcomes in a daily i.v. busulfan and fludarabine allogeneic transplant regimen. *Biol Blood Marrow Transplant*. 2008;14:220-228.
9. Bolinger AM, Zangwill AB, Slattery JT, et al. An evaluation of engraftment, toxicity, and busulfan concentration in children receiving bone marrow transplantation for leukemia or genetic disease. *Bone Marrow Transplant*. 2000;25:925-930.
10. Bredeson C, LeRademacher J, Kato K, et al. Prospective cohort study comparing intravenous busulfan to total body irradiation in hematopoietic cell transplantation. Blood Epub ahead of print September 30, 2013; doi:10.1182/blood-2013-08-519009.
11. Nagler A, Rocha V, Labopin M, et al. Allogeneic hematopoietic stem-cell transplantation for acute myeloid leukemia in remission: comparison of intravenous busulfan plus cyclophosphamide (Cy) versus total-body irradiation plus Cy as conditioning regimen-a report from the acute leukemia working party of the European Group for Blood and Marrow Transplantation. J Clin Oncol Epub ahead of print August 26, 2013; 10.1200/JCO.2013.48.8114.
12. Rezvani RR, McCune JS, Storer BE, et al. Cyclophosphamide followed by intravenous targeted busulfan for allogeneic hematopoietic cell transplantation: pharmacokinetics and clinical outcomes. *Biol Blood Marrow Transplant*. 2013;19:1033-1039.
13. Kato M, Takahashi Y, Tomizawa D, et al. Comparison of intravenous with oral busulfan in allogeneic hematopoietic stem cell transplantation wit myeloablative conditioning regimens for pediatric leukemia. *Biol Blood Marrow Transplant*. 2013;19:1690-1694.

(1) Background: Busulfan has been used as a conditioning regimen in allogeneic hematopoietic cell stem transplantation (HSCT). Owing to a large inter-individual variation in pharmacokinetics, therapeutic drug monitoring (TDM)-guided busulfan dosing is necessary to reduce graft failure and relapse rate.Â Therapeutic Drug Monitoring of Busulfan in Patients Undergoing Hematopoietic Cell Transplantation: A Pilot Single-Center Study in Taiwan. by. Rong-Long Chen.Â Collectively, the data demonstrated that TDM-guided busulfan-based conditioning is important for successful engraftment in Taiwan. 3. Discussion. When used in HCT conditioning, the busulfan cAUC has an extremely narrow therapeutic window. Allogeneic hematopoietic stem-cell transplantation for acute myeloid leukemia in remission: comparison of intravenous busulfan plus cyclophosphamide (Cy) versus total-body irradiation plus Cy as conditioning regimenâ€”a report from the acute leukemia working party of the European group for blood and marrow transplantation.Â Prospective cohort study comparing intravenous busulfan to total body irradiation in hematopoietic cell transplantation. Blood. 2013; 122: 3871-3878. PDF | On Oct 15, 2013, Christopher Bredeson published Intravenous versus Oral Busulfan-Based Conditioning for Pediatric Allogeneic Hematopoietic Cell Transplantations: Did The Pendulum Swing Too Far, Too Fast? | Find, read and cite all the research you need on ResearchGate.Â Pediatric Allogeneic Hematopoietic Cell Transplantations: Did The Pendulum Swing Too F ar, T oo F ast? Christopher Bredeson. * The Ottawa Hospital Blood and Marrow Transplant Program and Ottawa Hospital Research Institute, Ottawa, Ontario, Canada. Initially, hematopoietic stem cell transplantation (HSCT) was attempted in patients with severe combined immunodeficiency (SCID) as the only available curative treatment. It was a challenging procedure, associated with elevated rates of morbidity and mortality. Overtime, outcome of HSCT for PID has significantly improved due to availability of high-resolution HLA typing, increased use of alternative donors and new stem cell sources, development of less toxic, reduced-intensity conditioning (RIC) regimens, and cellular engineering techniques for graft manipulation.Â 1Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, United States. Treosulfan based conditioning is a safe and effective approach for children with hematological malignancies, including and importantly for infants and those patients undergoing second or later transplantation. Pediatr Blood Cancer Â© 2015 Wiley Periodicals, Inc. Citing Literature.