Standardising busulfan dosage for children and young adults

Lancet Haematol 2016
Published Online
October 13, 2016
http://dx.doi.org/10.1016/S2352-3026(16)30148-X
See Online/Articles
http://dx.doi.org/10.1016/S2352-3026(16)30114-4

In the evolving specialty of haemopoietic stem cell transplantation, whatever the source of stem cells and whatever the intensity of the conditioning regimen, busulfan has always been the major routine constituent of any pretransplantation regimen. It has been used in almost all types of haematological malignancies for which transplantation is needed, such as acute leukaemia and myelodysplastic syndromes, lymphomas, and myelomas.[1] Historically, in myeloablative regimens, 1 mg/kg oral busulfan was given every 6 h for 4 days to reach a total dose of 16 mg/kg.[2] Administration was unpleasant and sometimes resulted in vomiting. Furthermore, erratic gastrointestinal absorption caused unpredictable severe toxicity. For many years, what dosage of busulfan to use and how to reach the best efficacy:toxicity ratio have been key questions. Persisting relapses after allogeneic stem cell transplantation have led clinicians to increase the dosage, but this has been limited by toxicity, such as sinusoidal obstruction syndrome (potentially lethal), mucositis, and graft-versus-host-disease, resulting in increased non-relapse mortality.

Attempts have been made to identify optimum plasma concentrations with oral busulfan.[3] In particular, Slattery and colleagues[4] found that busulfan concentration in plasma determines graft survival and regimen-related toxicity. Most importantly, they noted that busulfan clearance, calculated from the area under the curve (AUC), declined with age during the first decade of life, which therefore precludes the use of a fixed dose for all ages, especially very young children. The introduction of an intravenous formulation of busulfan was a major improvement, resulting in a major decrease in the incidence of sinusoidal obstruction syndrome[5] and, in children, a significant improvement in the targeting of therapeutic window (87% with intravenous busulfan *vs* 56% with oral busulfan) and a significant decrease in variability of drug exposure.[6]

The calculation of the AUC after the infusion of the first dose of intravenous busulfan has become routine for further adjustment of the following doses in many centres, especially paediatric centres.[6] Unfortunately, no consensus exists on the best method of calculation, and although the association between busulfan exposure and toxicity has been widely studied, the effect of busulfan exposure on patient post-transplantation outcome has yet to be shown.

Imke Bartelink and colleagues' study,[7] in *The Lancet Haematology*, is important for several reasons. Even though it is retrospective, it included a large cohort of 674 paediatric patients, a difficult population in which busulfan clearance varies substantially with age. Patients were transplanted over 14 years in 15 major centres in Canada, Europe, and the USA. Comparison was made between the AUCs estimated by each centre (with various methods) on the one hand and, thanks to the availability of raw pharmacokinetic data, the recalculated AUCs by numerical integration using a non-linear mixed effect on the other hand. Not only was there no correlation between the two AUC assessments (r^2=0·35), but also the numerical recalculation defined an optimum busulfan AUC therapeutic window of 78–101 mg × h/L in children and young adults, which is narrower than previously thought, and was associated with fewer relapses (optimum AUC *vs* <78 mg × h/L AUC hazard ratio 0·57, 95% CI 0·39–0·84; p=0·0041) and an event-free survival of 77·0% (95% CI 72·1–82·9) at 2 years.

This work is important in a time when financial constraints have become worrying. Now that we know that intravenous busulfan, which is easier to administer than the oral formulation, is associated with improved event-free survival, if properly monitored, the additional cost of about €4000 per conditioning becomes negligible in view of the benefit achieved.

Indeed, already, intravenous busulfan has mostly replaced the oral administration.[8–10] In 2015, according to the registry of the European Society for Blood and Marrow Transplantation (EBMT), intravenous busulfan was given to 3939 (82%) of 4804 adult patients and 411 (84%) of 491 paediatric patients who received busulfan for an allogeneic transplantation. Whether this non-mixed effect numerical AUC assessment will become the standard tool worldwide and the optimum intravenous busulfan AUC found in the present study will become the recognised worldwide target remains to be seen.

Norbert-Claude Gorin
Department of Haematology and Cell Therapy, European Society for Blood and Marrow Transplantation, Paris Office, Hopital Saint-Antoine, Paris, France
norbert-claude.gorin@aphp.fr

I declare no competing interests.

1 Passweg JR, Baldomero H, Bader P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. *Bone Marrow Transplant* 2016; **51:** 786–92.

2 Santos GW. The development of busulfan/cyclophosphamide preparative regimens. *Semin Oncol* 1993; **20:** 12–16.

3 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:** 925–30.

4 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.

5 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 venoocclusive disease (HVOD), HVOD-related mortality, and overall 100-day mortality. *Biol Blood Marrow Transplant* 2002; **8:** 493–500.

6 Paci A, Vassal G, Moshous D, et al. Pharmacokinetic behavior and appraisal of intravenous busulfan dosing in infants and older children: the results of a population pharmacokinetic study from a large pediatric cohort undergoing hematopoietic stem-cell transplantation. *Ther Drug Monit* 2012; **34:** 198–208.

7 Bartelink IH, Lalmohamed A, van Reij EML, et al. Association of busulfan exposure with survival and toxicity after haemopoietic cell transplantation in children and young adults: a multicentre, retrospective cohort analysis. *Lancet Haematol* 2016; published online Oct 13. http://dx.doi.org/10.1016/S2352-3026(16)30114-4.

8 Gorin NC, Labopin M, Czerw T, Pabst T. Autologous stem cell transplantation for adult acute myelocytic leukemia in first remission: better outcome following busulfan and melphalan compared to busulfan and cyclophosphamide: a retrospective study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). *Cancer* (in press).

9 Nagler A, Labopin M, Gorin NC, et al. Intravenous busulfan for autologous stem cell transplantation in adult patients with acute myeloid leukemia: a survey of 952 patients on behalf of the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Haematologica* 2014; **99:** 1380–86.

10 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* 2013; **31:** 3549–56.