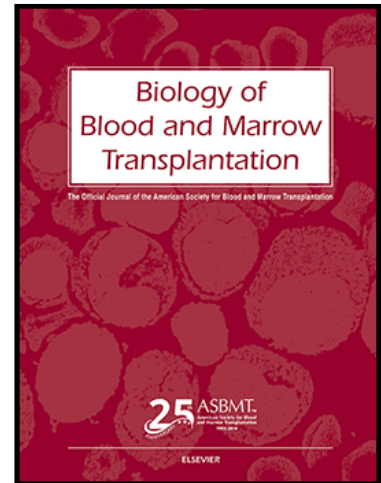


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PII: S1083-8791(20)30665-0
DOI: <https://doi.org/10.1016/j.bbmt.2020.10.011>
Reference: YBBMT 56185



To appear in: *Biology of Blood and Marrow Transplantation*

Received date: 4 September 2020
Accepted date: 7 October 2020

Please cite this article as: Delphine Veys , Persis Amrolia , Ajay Vora , Paul Veys , Anupama Rao , Michael Gattens , The Role of Blood and Marrow Transplantation in Treating Pediatric Chronic Myelogenous Leukaemia in the Era of Tyrosine Kinase Inhibitors, *Biology of Blood and Marrow Transplantation* (2020), doi: <https://doi.org/10.1016/j.bbmt.2020.10.011>

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The Role of Blood and Marrow Transplantation in Treating Pediatric Chronic Myelogenous Leukaemia in the Era of Tyrosine Kinase Inhibitors

Delphine Veys¹, Persis Amrolia², Ajay Vora³, Paul Veys², Anupama Rao³ and Michael Gattens⁴

¹St John's College Cambridge, UK

²Department of Blood and Marrow Transplantation, Great Ormond Street (GOS) Hospital for Children NHS Foundation Trust and Molecular and Cellular Immunology University College London GOS Institute of Child Health, London UK.

³Department of Haematology Great Ormond Street (GOS) Hospital for Children NHS Foundation Trust, London UK.

⁴Department of Haematology, Cambridge University Hospitals NHS Foundation Trust, Cambridge UK

Corresponding author: Professor Paul Veys

Department of BMT, Great Ormond Street Hospital for Children NHS Foundation Trust, London WC1N 3JH, UK.

Email paul.veys@gosh.nhs.uk

Key Words: Pediatric CML; TKI; BMT

To the editor,

The introduction of tyrosine kinase inhibitors (TKIs) in 2001 revolutionised the treatment of CML in adults, largely supplanting blood and marrow transplantation (BMT). Within 5 years these revolutionary drugs had also been approved for use in pediatric patients with CML. However, due to the low disease incidence and subsequent lack of robust clinical trial data in pediatric CML, the management of pediatric CML is largely extrapolated from adult data.

Hijiya et al. [1] outlined how paediatric CML exhibits more aggressive clinical features than adult CML, demonstrating accumulating evidence of the unique biology of the pediatric CML stem cell and host. This suggests a different approach may be required within the pediatric population.

With this in mind, Andolina and colleagues [2] designed and distributed a survey to pediatric hematologists/BMT consultants in the US/Canada to assess their willingness to recommend BMT for a patient with CML, based on various clinical scenarios. The results of this survey were then published in *Biology of Blood and Marrow Transplantation*. In accordance with adult practice and pediatric CML recommendations [3], their survey found that the majority of physicians only tend to recommend BMT after failure of first- and second-generation TKIs. In addition, they found there was significant interest in performing a clinical trial evaluating the safety and efficacy of stopping TKIs in children with CML who achieve and maintain a deep molecular response.

In light of these important findings and with permission from the authors we sent out this same survey to 140 pediatric haemato-oncologists and pediatric BMT specialists in the UK. We received 34 responses (24.3% response rate). The responses from the UK physicians were largely similar to those from the North American survey, although UK respondents showed an increased tendency to recommend BMT across all scenarios presented in the survey (see table 1). In line with current guidelines and the US survey, the majority of UK respondents recommended against BMT until failure of second TKI, with one notable exception. The majority 58.9% of UK respondents opted for BMT in a

2 year-old patient who relapsed during initial TKI therapy. Presumably this reflects the perceived lifetime burden of TKI therapy in such a young child and highlights the need for clear, age-specific criteria on when to proceed with BMT in young paediatric patients. Although there were no data presented from the US survey to compare against, UK respondents were more likely to recommend BMT (in the presence of a MUD donor) at an early stage in patients presenting in CML- Acute Phase (61.7%) and CML- Blast Crisis (84.8%).

	North American Survey	UK Survey
Recommend BMT for a patient with optimal response to initial TKI therapy	MSD: 8.0% MUD: 1.9%	MSD: 0% (16 yr old) 11.8% (2 yr old) MUD: not assessed*
Recommend BMT for a patient with an initial poor response to TKI	MSD: 40.2% MUD: 31.4%	MSD: not assessed* MUD: 35.1%
Recommend BMT for a patient who relapsed during initial TKI therapy	MSD: 36.5% MUD: 23.3%	MSD: 48.6% (16 yr old) 58.9% (2 yr old) MUD: not assessed*
Recommend BMT for a patient who met the response criteria for treatment failure during a second course of TKI therapy	MSD: 81.7% MUD: 69.8%	MSD: not assessed* MUD: 85.3%

Table 1: Comparison North American vs UK responses across four clinical scenarios.

* not assessed in 4 specific scenarios (included in supplementary table 1).

We postulated that the propensity for BMT in UK respondents may be due to a higher proportion of BMT specialists and/or physicians in service for >10 years, a correlation observed by Andolina et al. in the North American Study [2]. However, demographics between the surveys were comparable

(BMT specialists: 11.8% vs 13.8%, physicians in practice > 10 yrs: 44% vs 51% in the UK and North American surveys respectively).

Another interesting comparison to draw between the two surveys was the choice of initial TKI at diagnosis. Andolina et al. [2] found whilst the majority (67.4%) chose to start with imatinib, a significant minority (30.1%) chose to start with dasatinib. In contrast, 100% of respondents in the UK survey chose to start with Imatinib. This is most likely reflective of the cost restraints presented in the NHS.

Given the universal concern over long term TKI toxicity in children it is not surprising that the majority (86.7%) of North American respondents and 100% of UK respondents would consider participating in a clinical trial to assess the feasibility of stopping TKI therapy in children and adolescents with CP-CML who achieved a sustained MR 4.5 for >2 years.

A number of questions within the UK survey elicited a heterogeneous response. As an example, 32.3% of respondents said they routinely administer TKIs post-transplant for CML, whereas 36.2% do not, highlighting one of the existing controversies in managing paediatric CML. The heterogeneous responses within the UK survey, and the subtle but important differences observed between the two surveys confirms the need for further research and evidence-based, pediatric specific guidelines for the optimal management of children and adolescents with CML.

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