

## ORIGINAL ARTICLE

## Current European practice in pediatric myeloablative conditioning

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**Myeloablative conditioning continues to be employed in hematopoietic stem cell transplantation among patients with pediatric transplant indications. Fractionated TBI (fTBI) remains, with its considerable anti-leukemic potential, the cornerstone of conditioning in the most common of pediatric indications, ALL in its first, second or subsequent remission despite its well-established long-term sequelae. The feasibility of chemotherapy-only regimens has been established and these regimens widely employed in other pediatric indications, for example, in ALL below the age of 2 years, AML, myelodysplasias or severe aplastic anemia. Conditioning regimens are being modified with data accumulating on the role of, for example, pre-transplant residual disease, advanced HLA-typing or haploidentical transplantations in the pediatric setting.**

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**Introduction**

Depending on the disease in question as well as the stem cell source, two goals need to be attained by the preparative regimen prior to hematopoietic stem cell transplantation. With the majority of allogeneic transplants being performed on patients with a malignant disease, one of the key goals of conditioning is a reduction of the malignant cell mass, ideally down to disease eradication. In the allogeneic setting, the preparative regimen also needs to be immunosuppressive enough to secure engraftment without graft rejection. Most preparative regimens employed have initially been designed for adult recipients with a hematologic malignancy.

**Acute lymphoblastic leukemia**

TBI, fractionated (fTBI) in most cases and combined with CY, has been extensively employed due to its substantial immunosuppressive potential, lack of cross-reactivity with other modalities and sanctuary sparing as well as effective antileukemic potential as the backbone of the conditioning regimen in transplants performed for pediatric ALL<sup>1–7</sup> in the matched related, matched unrelated and mismatched settings. Cumulative doses up to 10–14 Gy have been used with many groups reducing the pulmonary cumulative dose down to 8–9 Gy and the use of fTBI to patients above the age of 2 years.

fTBI continues to be employed in the pre-transplant conditioning of pediatric patients with ALL by most groups with many currently combining it with etoposide (60 mg/kg) for patients above the age of 2–3 years.<sup>8–12</sup> Yet, the use of fTBI in conjunction with CY also continues.<sup>13</sup> The clinical efficacy of chemotherapy-only regimens over fTBI-containing regimens in the conditioning of patients with ALL and over the age of 2 years has not been established.<sup>7</sup>

For patients above the age of 2–3 years but not eligible for fTBI (for example, those with a history of high-dose irradiation), chemotherapy-only regimens (for example, BU/CY/melphalan (Mel)) are employed.<sup>12</sup>

fTBI-based regimens have been employed also among patients under the age of 18 months, particularly in the unrelated setting.<sup>14</sup> Yet, to avoid the long-term toxic effects of fTBI, most groups currently employ chemotherapy-only regimens for the youngest patients under the age of 2–3 years as is also the recommendation of the Interfant-group for those under the age of 1 year. Variable drug combinations are used in this group with most having a BU + CY backbone in combination with, for example, Mel, thiotepea, etoposide or alemtuzumab.

**Acute myeloid leukemia**

Non-fTBI-based regimens are currently employed by most groups for patients transplanted for AML in either first or subsequent remission. Regimens with a BU + CY backbone are mostly used and supplemented in most cases with Mel.<sup>15</sup> Yet, fTBI-containing regimens are also being employed by some groups, particularly in advance cases.<sup>16</sup> No data

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comparing these two approaches in the treatment of pediatric AML are available. The International-BFM-Study Group presents the two key preparative regimens (that is, BU + CY + Mel vs fTBI + CY) as optional in their ongoing trial on relapsed AML.

### MDS and juvenile myelomonocytic leukemia

In the pretransplant conditioning of this challenging group of pediatric patients, both chemotherapy-only (BU + CY + Mel) and fTBI-containing regimens have been employed, with the former rendering a seemingly lower incidence of non-relapse mortality.<sup>17,18</sup>

### Fanconi anemia

In this toxicity-prone group of patients, convincing data are available on the use of low-dose CY (20 mg/kg) and thoraco-abdominal irradiation (5 Gy) as conditioning, when sibling donors are employed.<sup>19</sup> Data on the use of CY-only regimens are also available, but only on more limited numbers of patients.<sup>20</sup>

In the unrelated donor setting, medium-dose CY (40–45 mg/kg) in combination with either thoraco-abdominal or fTBI and anti-T serotherapy has been successfully employed.<sup>21</sup> More recently, a reduction in treatment-related toxicity has been reported, when fludarabine-containing regimens (mostly also containing fTBI (4.5 Gy) with CY) were used.<sup>22</sup>

### Severe aplastic anemia

For severe aplastic anemia, and again to reduce TBI-related long-term sequelae, most groups currently employ non-fTBI-containing regimens, CY with or without ATG in the sibling donor setting<sup>23</sup> and fludarabine plus cyclo plus ATG in the unrelated setting.<sup>24</sup> Some employ fludarabine-containing regimens also in the sibling setting as an essentially non-myeloablative approach. TBI (2–6 Gy) with cyclo ± fludarabine and ATG are also being used by some groups in the unrelated donor setting. Even in the face of an increased risk of graft rejection in stem cell transplantation for pediatric severe aplastic anemia, encouraging data on the use of partial T-cell depletion have been reported.<sup>25</sup>

### Additional indications

For patients with primary immunodeficiencies, both data and the recommendations of both The European Group for Blood & Marrow Transplantation and the European Society for Immunodeficiency support the use of BU and CY with effective T-cell depletion particularly in the mismatch setting.<sup>26</sup>

In stem cell transplantation for inborn errors of metabolism, a variety of preparative regimens have been employed, but no preferred regimen has been identified.<sup>27</sup> The feasibility of standard BU + CY regimen has been

demonstrated in transplantations in the case of, for example, mucopolysaccharidosis type 1H (Hurler).<sup>28</sup>

### Haploidentical transplants

In haploidentical transplantation for pediatric acute leukemia, both standard fTBI-based regimens and BU with CY and thiotepa have been successfully employed in conjunction with the obligatory high dose of CD34+ cells and low dose of CD34+ cells.<sup>29,30</sup>

### Specific issues

While the benefits of *in vivo* and/or *ex vivo* T-cell depletion in reducing the incidence and severity of both acute and chronic GvHD<sup>31</sup> as well as in increasing the number of potential donors<sup>1,25</sup> have been well established, the use of T-cell depletion in the matched unrelated donor setting of pediatric stem cell transplantation remains controversial with data on both an increased risk of relapse<sup>32</sup> and viral infections<sup>33</sup> having been published. Most European groups employ ATG or alemtuzumab (Campath) in matched unrelated transplantation for pediatric ALL and AML.

With cord blood transplantation, mostly standard fTBI-based regimens have been employed.<sup>34</sup>

### Future perspectives

Several key developments are underway that will affect the structure and composition of future conditioning regimens. These include accumulating data on the role of minimal residual disease prior to transplant in defining the risk of relapse post transplant, data on the effects of advanced HLA-genotyping on our perception of HLA compatibility, the increasing use of peripheral blood as the stem cell source also in the pediatric setting, the use of haploidentical donors and accumulating data on the pathophysiology of both acute and chronic GvHD as well as those on the process of immunoreconstitution post transplant. The result will, in all likelihood, be an ever more 'tailored' approach on conditioning based on the biological and disease characteristics of a given patient.

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### Conflict of interest

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