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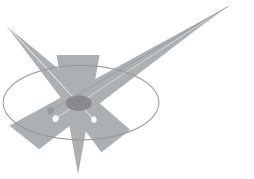

Review Paper

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Infectious complications in children conditioned for allogeneic haematopoietic stem cell transplantation with reduced intensity conditioning or with treosulfan-based reduced toxicity preparative regimen

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background To expand access to allogeneic haematopoietic stem cell transplantation (allo-HSCT) to patients who are ineligible for conventional myeloablative FTBI- or busulfan-based preparative regimens, the idea of reduced intensity conditioning (RIC) in the early 1990s, and somewhat later in the late 1990s the idea of treosulfan-based reduced toxicity conditioning, were created. However, there is still need for further optimization of the conditioning regimen for allo – HSCT, which should demonstrate sufficient myeloablative, immunosuppressive and anti-tumour effects (in the case of malignant disease) along with low early and late transplant-related mortality.

Aim Comparison of infections occurring in children prepared for allogeneic HSCT with reduced intensity conditioning (RIC) and treosulfan-based reduced toxicity conditioning regimen (TREO-RTC).

Material/Methods Data concerning infections in patients conditioned for allogeneic-HSCT with RIC and reported in references found using the PubMed database were compared with data concerning 51 children prepared for allogeneic HSCT with TREO-RTC and reported by Grund et al. (2006).

Results Following RIC-HSCT the majority of infections occurred beyond day +30. Bacteria are leading agents causing infections. The pattern and incidence of fungal infections are comparable to those observed after myeloablative conditioning, whilst incidence of EBV-reactivation and EBV-related disease is increased, but BK-viruria is less common. Reported 1-year mortality related to infections after RIC-HSCT is around 10%. In 51 children conditioned with TREO-RTC the profile, incidence and timing of infections were comparable to those observed after conventional regimens (Grund et al., 2006). Three (5.9%) of them died due to infectious complications, one (1.9%) before day +100, and 2 (3.9%) late after transplantation in the course of extensive chronic GvHD.

Conclusions Infections remain an issue in children undergoing allogeneic HSCT after RIC or TREO-RTC. Therefore prophylaxis, surveillance, early diagnosis and pre-emptive treatment of infections still play an important role in supportive care after RIC- and TREO-RTC-HSCT. This approach should be adjusted to the immune

reconstitution profile related to immunosuppressive intensity of the regimen and GvHD prophylaxis, donor type, donor/recipient pretranspant viral status, stem cell source and GVHD occurrence. Standardization of supportive care after RIC- and TREO-RTC-HSCT, related to factors which determine risk of infections, is needed.

Key words **allogeneic haematopoietic stem cell transplantation • reduced intensity conditioning • treosulfan-based reduced toxicity regimen • infectious complications**

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Background

To expand access to allogeneic hematopoietic stem cell transplantation (allo-HSCT) to patients who are ineligible for conventional myeloablative FTBI- or busulfan-based preparative regimens, the idea of reduced intensity conditioning (RIC) in the early 1990s [1–3], and somewhat later in the late 1990s the idea of treosulfan-based reduced toxicity conditioning, were created [4,5].

RIC is defined as a regimen demonstrating little or no myelosuppression along with intense immune suppression sufficient to prevent an immediate rejection of allogeneic haematopoietic stem cells and potency to create an environment for long-term donor-derived haematopoiesis by donor lymphocytes, which – in recipients with malignancy – provide an anti-tumour effect that maintains disease remission [6]. In practice, RIC regimens are characterized by: 1) reversible myelosuppression (usually within 28 days) without stem cell support; 2) mixed chimerism in a proportion of patients at the time of first assessment, and 3) low rates of non-haematological toxicity [7]. Usually RIC consists of one or more of the following components: 1) ⩽500cGy TBI; 2) ⩽9mg/kg total busulfan dose; 3) ⩽140mg/m^2 total melphalan dose, and/or 4) ⩽10mg/kg total thiotepa dose [6]. Thus, different RIC regimens should not be considered equivalent, since their anti-neoplastic efficiency, and their impact on chimerism and immune reconstitution, may be different. Over the last 5 years the use of RIC regimens for allo-HSCT has increased significantly. According to the last report of CIBMTR among 13107 registered recipients <20 years of age 716 (5.5%) have been prepared for allo-HSCT with RIC [8]. According to the Third EBMT/AMGEN Workshop on RIC Allogeneic HSCT [9] there is already evidence that: 1) RIC-HSCT is feasible for both malignant and non-malignant diseases, 2) after RIC-HSCT and engraftment with long-lasting complete donor chimerism can be achieved in the majority of patients, 3) there are few graft rejections especially when BM is used for RIC-HSCT, 4) there is reduction of long-term toxicities after RIC-HSCT, 5) post RIC-HSCT long-lasting responses (>3 years) can be achieved in malignant and non-malignant diseases, but 6) acute and chronic GvHD, as well as 7) infectious complications remain an issue after RIC-HSCT. The last two factors, i.e. GvHD and infections, are the most common obstacles to successful outcome of RIC-HSCT [10,11].

Therefore, there is still a need for further optimization of the conditioning regimen for allo-HSCT, which should demonstrate sufficient myeloablative, immunosuppressive and anti-tumour effects (in the case of malignant disease) along with low early and late transplant-related mortality. Availability of such a preparative regimen is crucial in children and adults with significantly increased risk of life-threatening conventional regimen toxicity due to organ injury related to primary disease, comorbidities and/or previous treatment (including previous autologous or allogeneic HSCT).

As demonstrated previously by Casper et al. in adults [12] and by Wachowiak et al. in children

[13] these aims of an optimal preparative regimen seemed to be – at least to a significant extent – achieved with treosulfan-based reduced toxicity conditioning (TREO-RTC). In contrast to RIC regimens, TREO-RTC demonstrates total or at least subtotal myeloablative effect and standard immunosuppressive effect, but still low organ toxicity and satisfactory anti-malignancy effect. Recently Grund et al. [14] analysed infectious complications in children undergoing allo-HSCT after conditioning with treosulfan.

Aim

Comparison of morbidity and mortality related to infectious complications in children prepared for allo-HSCT with reduced intensity conditioning (RIC) and with treosulfan-based reduced toxicity conditioning (TREO-RTC).

Materials and Methods

Data concerning infectious complications in patients conditioned for allogeneic HSCT with RIC and reported in references found using the PubMed database were compared with such data concerning 51 children reported on behalf of the Polish Paediatric Group for HSCT by Grund et al. [14], and 30 adult patients published by Casper et al. [12] prepared for allo-HSCT with TREO-RTC.

Results

Infectious complications in children conditioned for allogeneic haematopoietic stem cell transplantation with reduced intensity conditioning regimen

In general, RIC regimens were associated with lower rates of severe toxicity and non-relapse mortality but, still one-year non-relapse mortality (NRM) in patients of the RIC regimen was significant and amounted to 16% [6,10,11]. In contrast to patients undergoing conventional myeloablative regimens, in whom most deaths related to transplant procedure are observed within first 3 months after HSCT, among the recipients of RIC regimens majority of deaths occured later, i.e. between 3 and 6 months post transplantation. The most common obstacles to successful outcome of RIC-HSCT are GvHD and infections. Reported 1-year mortality related to infections after RIC-HSCT is around 10%.

After RIC-HSCT till day +30 the neutropenic fever was observed in 38% of patients [15], however the majority of infections occured beyond day +30, and at one year 77% patients developed any infection [16]. Overall risk of infection is higher after RIC-HSCT from an alternative donor. Bacteria were the leading agents causing infections, and the occurrence of bacteriemia at one year is 55%, which was mainly caused by coagulase-negative staphylococci, and other Gram-positive bacteria [16]. The pattern and incidence of fungal infections were comparable to those observed after myeloablative conditioning [17]. In contrast, following paediatric stem transplantation with RIC the incidence of EBV-reactivation and EBV-related disease was significantly increased, particularly in children with selective depletion of recipient T cells following the use of ATG [18–20]. BK-viruria and haemorrhagic cystitis were less common in patients receiving RIC [21]. Risk of CMV infection was increased in patients with high-risk CMV serology [16]; however, its incidence, like the incidence of other non-bacterial infections, correlated with the use of corticosteroids (Frere, 2006). In non-myeloablative HSCT patients the onset of CMV infection was significantly delayed in comparison to those receiving the myeloablative regimen (day +130 versus day +52), but its overall 1-year incidence was similar in both groups of patients [22].

Infectious complications in children conditioned for allogeneic haematopoietic stem cell transplantation with treosulfan-based reduced toxicity conditioning regimen

Recently Grund et al. [14] demonstrated the low infection-related death rate in children undergoing allo-HSCT after reduced toxicity conditioning with treosulfan (TREO-RTC). Between 2000 and 2005 a total of 51 children, including 42 with haematological malignancies and 9 with congenital disorders, were prepared for allo-HSCT with TREO-RTC. Out of 42 patients with usually advanced haematological malignancies 19 obtained HSCT from a matched sibling donor (MSD), and 23 from a matched unrelated donor (MUD). Among 9 children with congenital diseases 5 were transplanted from MSD, and 4 from MUD. As the preparative regimen TREO ($3\times10^{-14}g/m^2$) was given i.v. in various combinations with other cytostatics according to diagnosis, risk factors of regimen-related toxicity and/or regimen used for first HSCT. Prior MUD-HSCT and in all patients with congenital disorders ATG (n=27) or Campath (n=4) was given. GvHD prophylaxis usually consisted of cyclosporine A (CsA) and mehotrexate (MTX) (n=24) or CsA (n=18).

Infections with high risk of reactivation or progression occurred prior to HSCT in 16 (31.4%) patients. One child was conditioned and transplanted in the course of pneumonia.

By day +100 in 42 children with malignancy 38 infections were documented, including 22 viral (52%), 10 bacterial (24%) and 5 fungal (12%). Fever of unknown origin (FUO) was observed in 5 (12%) patients. One (2.4%) early infection-related death occurred in a patient who after MUD-HSCT developed adenovirus infection with multiorgan failure (day +66). In addition 2 (5%) patients died late after MUD-HSCT in the course of chronic GvHD due to fungal infection (day +634 and +865). By day +100 among 9 children with congenital disorders 8 (89%) demonstrated 13 episodes of infection, including 6 viral (46%), 6 bacterial (46%), and one fungal (8%). In patients transplanted for congenital disorders neither early nor late infection-related deaths occurred. Altogether, three (5.9%) out of 51 patients studied died as a result of infectious complications, including one (1.9%) before day +100, and 2 (3.9%) late after transplantation (both in the course of extensive chronic GvHD).

Discussion

The lack of beneficial effect of RIC on incidence of infectious complications may be related to the type of patients selected for the regimen, who usually demonstrate high risk of reactivation of previous infections. Apart from that RIC regimens as well as intensive, usually double GvHD prophylaxis demonstrate highly immunosuppressive effects. In addition, despite of mentioned above intensive GvHD prophylaxis, RIC-HSCT there is a high risk of both acute and chronic GvHD with, in addition, so-called "late-onset acute GvHD" (after day +100), which may overlap with chronic GvHD [23], and results in an increased risk of infections by itself. The increased incidence of EBV-related disease following paediatric stem cell transplantation with RIC probably reflects the profound immunosuppressive effect of this type of conditioning, together with the incomplete ablation of recipient-derived B cells [18]. It was also demonstrated that the use of alemtuzumab *in vivo* in non-myeloablative conditioning may result in a delay in EBV-specific T-cell recovery [24].

As for TREO-RTC, the profile, incidence and timing of infections observed in children conditioned for allo-HSCT were comparable to those observed after conventional regimens. Despite the high risk of transplant-related complications observed before HSCT, the rate of fatal infections in the studied group of children was low, in both early and late post-HSCT periods. However, according to Casper et al. [12] among 30 adult patients suffering from haematological malignancies and prepared for allo-HSCT with TREO-RTC, the incidence of non-relapse deaths related to infection (unknown origin, days +29, +87 and +112) was 10%, i.e. identical to the one reported after RIC-HSCT.

Conclusions

Infections remain an issue in children undergoing allogeneic HSCT after RIC or TREO-RTC. Therefore prophylaxis, surveillance, early diagnosis and pre-emptive treatment of infections still play an important role in supportive care after RIC- and TREO-RTC-HSCT. This approach should be adjusted to immune reconstitution profile related to immunosuppressive intensity of regimen and GvHD prophylaxis, donor type, donor/recipient pre-transplant viral status, stem cell source and GVHD occurrence. Standardization of supportive care after RIC- and TREO-RTC-HSCT related to factors which determine the risk of infections is needed.

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