STRATEGY OF CONDITIONNING THERAPY FOR HEMATOPOIETIC CELL TRANSPLANTATION

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SUMMARY

The rationale behind the use of different conditioning protocols in allotransplanted patients is given. Standard based on Busulfan (Bu) and Cyclophosphamide (Cy) chemotherapy protocol was used for good risk patients and those with a positive history of liver malfunction. In poor risk patients Bu and Cy was supported by ether Etoposide (VP-16) or Thiotepa. Toxicity of the VP-16 consiting chemotherapy was considerably higher than that of BuCy alone. This resulted in a higher transplant related mortality in VP-16 receiving patients. In aplastic anemias (AA) in children Cy was effective in a dose of 200 mg/kg b.w. given prior transplantation. In poor risk patients with severe AA anti-thymocyte globulin (ATG) was used. In Fanconi anemia ATG plus low dose of Cy proved to be succesful in 4 transplanted cases.

INTRODUCTION

Conditioning of allogeneic bone marrow/blood transplantation is based on radio/chemo-therapy. This treatment should secure optimal myeloablation, cytoreduction of malignancy in neoplastic diseases and immunosuppression preventing host versus graft reaction. The treatment varies in neoplastic and non-neoplastic diseases and depends on stage of disease (early, intermediate or advanced) and the extent of donor recepient disparity. In this presentation we are sharing with you our experience in the use of chemical conditioning.

STANDARD RISK PATIENTS WITH HEMA-TOLOGICAL MALIGNANCIES

Busulfan (Bu) and Cyclophosphamide (Cy) is a backbone of our procedure. In standard risk patients with hematological malignancies the usual dose of Bu (4 x 4 mg/kg b.w.) is adjusted accordingly to the expected higher metabolic rate in children (Regazzi et al. 1993) (4 x 5 mg/kg b.w. in age < 3 yrs) . In children and adults cumulative dose of 200 mg/kg b.w. of Cy is routinely given during 4 days (BuCy4). In cases with higher risk of veno-occlusive disease or other hepatic complications, Cy may be administered in a cumulative dose of 120 mg/kg b.w. in two days time (BuCy2) and Etoposied can be omitted (toxicity) in spite of more advanced stage of disease (6 patients in our group). 20 patients have already been allografted in our institution with the use of BuCy4 conditioning regimen. The group consisted of 13 patients in early and 7 in intermediate/advanced stage of disease. In all cases (except 1) who received BuCy4, hematological reconstitution was observed. Blood group serology confirmed complete chimerism in all evaluable cases. Among BuCy4 patients relapse was observed in 2 out of 20 cases (time of relapse: +100, +217 d).

POOR RISK PATIENTS WITH HEMA-TOLOGICAL MALIGNANCIES.

To this category belonged patients with hematological malignancies in intermediate and advanced stage or poor laboratory or clinical prognostic factors. Among 47 patients transplanted in our Unit 30 fulfilled criteria of poor risk. All of them except 7 who received BuCy4 , as explained above) were given more ggressive chemical conditioning. Two protocols are actually in peration. One includes Etoposide (VP-16), the other - Thiotepa TT), as adjuvants to BuCy.

1. VP-16 consisting regimen.

The cumulative dose of VP-16 ranges from 15 to 30 mg/kg b.w. , Bu is not curtailed but Cy is given in a dose of 120 mg/kg b.w. This regimen

was associated with considerable toxicity. Frequency of rash and skin pigmentation as well as elevation of serum bilirubine level was higher in comparison to BuCy4 protocol. This toxicity may promote accumulation of inflammatory cells in involved tissues, hence promoting reactivity against skin and intestine associated antigens. Frequency of aGvHD among patients receiving VP-16 consisting chemical conditioning was higher than in BuCy4 group . This association may be merely indirect. VP-16 treated patients were in more advanced stage of disease. This is associated with a higher cumulative dose of chemotherapy and related to this treatment toxicities, what in turn increases the risk of viral infections. Altogether transplant related mortality was higher among patients with more advanced disease receiving VP-16 as a part of conditioning regimen than in BuCy4 group (37% vs 20%). Number of relapses was rather low in this group of patients (2 out of 24 patients). More aggressive chemotherapy decreased the higher risk of relapse expected in more advanced cases. 2. Thiotepa consisting regimen. BuCy4 with or without VP-16 appeared to be less effective in more advanced acute lymphoblastic leukemia in children than total body irradiation (TBI). To increase tumorocidal activity of chemotherapy (v. Beultzingsloewen et al., 1995) Thiotepa (TT) was chosen as a part of conditioning regimen in high risk patients with hematological malignancies. TT was primarily used in our Unit as part of chemotherapy in a child with medulloblastoma. This treatment consisted of Bu (4 x 150 mg/m2) TT (3 x 300 mg/m2).
Acceptable toxicity was observed with good tumor response. This positive experience prompted us to use TT according to the protocol obtained from the Virchow's Klinikum Humboldt Univesity in Berlin. Altogether 3 patients with advanced stages of CML and ALL were treated.
Aplastic anemia

STANDARD RISK SEVERE APLASTIC ANEMIA.

Cy alone in a dose of 200 mg/kg b.w. was used as conditioning regimen in 5 children. In all cases marrow take was documented. Toxicity of this procedure was neglegible and consequently no transplant related complications were seen. This procedure is not sufficient for patients with multiple transfusions what we experienced in 45 yrs old adult who failed to recover after BMT and ultimately died due to the septic complicaion.

POOR RISK APLASTIC ANEMIA.

In this group of patients identified by long standing disease and/or previous blood transfusions, anti-thymocyte serum was used in addition to Cy (Storb et al., 1994). The protocol is based on Cy (4 x 50 mg) and anti-thymocyte globulin (ATG, Fresenius: 5 x 5 mg). ATG brings risk of CMV reactivation. Ganciclovir may be used as prophylaxis of Herpes viruses reactivation. Alternatively, twice weekly repeated surveillance of CMV antigen in mononuclear cells can justify the use of Ganciclovir in prevention of apparent clinical manifestation of CMV reactivation.

FANCONI ANEMIA (FA).

This disease is characterised by chromosomal instability due to theimpairment of free radical scavenger system. Literature data documented a high risk of epithelial cancer in patients with FA receiving irradiation as a part of conditioning regimen (Deeg et al., 1996). To avoid this complication our conditioning protocol is based on the use of ATG and low dose Cy. Four children were transplanted so far. They received: ATG (Fresenius, from 5mg to 15mg per day for five consecutive days) and Cy (4 x 20 mg). In all these cases transplantation proved to be successful with prompt
hematological recovery and without any life-threatening complications.

ALTERNATIVE TRANSPLANTATIONS AND HIGH RISK AGVHD PATIENTS.

In alternative haploidentical transplantations two modalities were chosen. In patients transplanted from HLA phenotypically donors conditioning may not differ from that used in standard risk patients.
In phenotypically identical but genetically different transplantation ATG together with BuCy4 was used to increase the level of immunosuppression. However, this approach may not be sufficient. In 44 yrs old patient with CML in accelerated phase grafted from his mother (75 yrs old, who differed in DR4 allelic subspecificity) with peripheral blood progenitor cells a fatal aGvHD appeared at the time of hematological recovery.
T cell depletion is more effective for aGvHD prevention. However, removal of T cells from the graft decreases the efficacy of transplantation in some hematological malignancies especially in

CML. Some compromise must be achieved in these cases between the risk of aGvHD and benefit of GvL. In haploidentical transplantation in SCID case (transplanted from his mother) T cells were depleted with Campath 1M monoclonal antibody. This purging, however, did not prevent progression of preexisting in this particular case materno-fetal GvHD. In some situations T cell depletion with monoclonal antibodies may be too rigorous affecting bone marrow take. Recently in 46 yrs old male patient transplanted from his 52 yrs, multiparous sister (HLA and MLC matched) CD2+ cells were depleted from the graft with the use of an appriopriate monoclonal antibody and baby rabbit complement. Hematological reconstitution was apparent in bone marrow aspirates +10 and +15 days after transplantation and the patient reached 500 granulocytes/ul on 21 day after grafting.

CHEMICAL CONDITIONING vs TBI and C1y.

In our series of patients TBI was not used. Literature data rather failed to document the superiority of any of these two procedures with respect to the event free survival (Blume et al. 1993, Santos 1993). The outcome of the procedure is affected by the stage of malignant disease, level of alloimmunization prior to transplantion, especially in aplastic anemia cases and level of disparity in alternative and matched unrelated donor (MUD) transplantations. There are different toxicities of TBI and chemical conditioning with rather higher risk of VOD in the latter treatment protocol and pneumonitis in TBI patients. In some clinical situations TBI may be superior. Our own work suggests that standard BuCy with or without VP-16 is inferior in comparison to TBI in more advanced ALL cases (Wachowiak et al., 1995). Therefore, in our current approach we favour TT containing regimen and cranial irradiation prior to chemical conditioning. The other point of our concern is liver toxicity in HBV and/or HCV positive cases. Unfortunatelly a proportion of patients referred to our unit for allotransplantation were infected with HBV or HCV. More aggressive chemical conditioning is associated with a higher incidence of hepatic toxicity (Nevill et al. 1991). Patients with history of viral hepatitis can benefit from TBI more than those not affected by hepatitis viruses. Drawbacks of not using TBI seem to be partly compensated by rather low incidence of CMV pneumonitis which was seen only in one out of 64 transplanted patients. Chemical conditioning and TBI should be used accordingly to the clinical needs (Ringden et al. 1994) and this is taken into consideration in planning further development of alloBM/Blood transplantations in our institution.

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