Conditioning regimen using Busulfan plus melphalan in hematopoietic stem cell transplantation: can this conditioning regimen be used in autologous or allogeneic transplantation for acute leukemia?

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The majority of patients with acute myeloid leukemia (AML) achieve complete remission (CR) after induction/consolidation chemotherapy. The optimal post-remission treatment is still a matter of debate. However, the intensification of post-remission treatment, including high-dose chemotherapy followed by infusion of autologous or allogeneic stem cells, has progressively increased, considering the high risk of relapse without any further post-remission therapy.

The most effective conditioning regimen before hematopoietic stem cell transplantation (HSCT) remains controversial. The combination of busulfan and cyclophosphamide (BU-Cy) is the most used conditioning treatment as its anti-leukemic activity is well established.

However, the need to analyze novel conditioning regimens has recently grown due to the high extra-hematological toxicity and the immunosuppressive potential of the Bu-Cy regimen.

For example, Cy is a widely used antineoplastic agent, but, at high doses, potentially life-threatening side-effects such as hemorrhagic cystitis (HC) need multidisciplinary and individual approaches to prevent and cure these devastating complications.

Melphalan (Mel) is a bifunctional alkylator with a broad spectrum of activity in a variety of hematological malignancies. High-dose Mel[1] followed by autologous stem cell transplantation (ASCT) has extensively been used in patients with multiple myeloma (MM), other lymphoid malignancies, such as relapsed or refractory lymphomas and acute lymphoblastic leukemias as well as a salvage regimen for relapsed AML patients. High-dose Mel has also been used in AML patients undergoing allogeneic HSCT in combination with fludarabine for reduced intensity conditioning regimens.

Moreover, high-dose Mel with ASCT has been used as intensive therapy[2] in childhood AML in first complete remission with results comparable to those obtained with total body irradiation (TBI) or BU-containing regimens.

Mel was selected considering its relatively low extra-hematological toxicity compared with Cy or TBI. High-dose Mel followed by ASCT as salvage treatment in untreated relapsed AML patients is associated with mild to moderate toxicity, similar to what is expected in MM patients receiving the same chemotherapy regimen.

In most studies,[3,4] conditioning regimens with high-dose Mel were well tolerated both in adults and in pediatric patients, with no toxic death, veno-occlusive disease or life-threatening complications. In the pediatric setting, the incidence of treatment-related mortality (TRM) was reported to be much lower with high-dose Mel, even in combination with TBI when compared with BU- or Cy-based conditioning regimens.

Furthermore, the prevention of long-term effects, especially in the pediatric setting, is a major issue. Thus, hypothyroidism, growth impairment and cataract formation have been associated with TBI regimens, while sterility has been described after both TBI and BU therapies. With high-dose Mel, mild dysfunction of the thyroid and gonads were observed only in association with constitutional dysfunctions such as Down's syndrome.

The bi-functional DNA-alkylating Agent, Bu is now widely used as an alternative to TBI in the conditioning therapy for HSCT. Concerns about delayed growth and retarded intellectual development have been associated with the use of TBI in children, and this finding has influenced a gradual shift to chemotherapy-only conditioning in pediatric transplantation. Bu has frequently been included in conditioning regimens used in pediatric HSCT since the early 1980s when the Bu/Cy regimen was introduced.

In the efforts to develop more effective and less toxic high-dose chemotherapy regimens, it was hypothesized that alkylating agents, which form the backbone of most pre-transplant regimens, can overcome cellular resistance to chemotherapy based on their multiple intracellular targets. Thus, several research groups evaluated the combination of Bu and Mel. Neither of these alkylators needs to be activated, and they

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both display linear pharmacokinetics in the dose range(s) usually employed. Furthermore, the good central nervous system (CNS) penetration of both Bu and Mel and their relative non-overlapping clinical toxicity profiles should make this combination an effective, high-dose chemotherapy regimen.

In the autologous setting,[4,5] BU plus Mel as conditioning regimen prior to ASCT has been administered in patients affected by MM, lymphoid malignancies and AML in first CR. Results from various studies[4,5] including combinations of these drugs, suggest that the BU-Mel regimen is effective and well tolerated. The most relevant extra-hematological adverse event was oral mucositis. The two formulations of BU (oral and intravenous) did not show any difference either in the toxicity profile or for the anti-leukemic activity.

Few data are available on the use of this conditioning regimen in allogeneic stem cell transplantation. In some studies, intravenous Bu in combination with Mel was administered in ALL and advanced lymphoma. This combination appeared to be well tolerated with disease control as good as would be expected with a TBI/Cy regimen. Furthermore, the use of the Bu-Mel-ATG (antithymocyte globulin) regimen was reported as conditioning for unrelated umbilical cord blood transplants in pediatric patients. Again, the regimen was well tolerated and the engraftment of granulocytes was achieved in a good proportion of patients with a satisfactory overall survival.

Taken together, these data suggest that the role of the Bu-Mel combination as a conditioning regimen prior to HSCT is promising in patients with hematological malignancies.

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