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THYMOGLOBULIN AS PART OF THE PRE-TRANSPLANT CONDITIONING FOR UNRELATED DONOR STEM-CELL TRANSPLANTATION A DOSE-FINDING STUDY

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To find the optimal dose of Thymoglobulin as part of the conditioning, de-escalating doses of Thymoglobulin was given to 169 consecutive stem cell transplantation (SCT) patients with an HLA-compatible unrelated donor. Initially a total dose of 10 mg/kg was used (n=67). The total dose was then lowered to 8 mg/kg (n=24), 4 mg/kg (n=54) and finally to 6 mg/kg (n=24). Patients were divided into three groups: a high dose (10 mg/kg), an intermediate dose (6-8 mg/kg) and a low dose group (4 mg/kg). Patient characteristics differed between the three groups as follows: the intermediate dose group included fewer patients in CR1/CP1, the low dose group had the highest median patient age while the high dose group received a lower nucleated cell-dose. Conditioning consisted either of Bu16/Cy120 or Cy120/TBI10Gy, and most patients received CsA+MTX as GVHD prophylaxis. Results. The incidence of acute GVHD grades III-IV decreased with increasing dose of Thymoglobulin. TRM was similar in the high and low dose, while the intermediate dos showed a non-significant lower TRM rate. Among patients with acute leukaemia (n=104), the lowest relapse rate and the best RFS was seen in the intermediate dose group. Patients with CML (n=38) were only divided into a high (>6 mg/kg) and a low dose group (>6 mg/kg) due to low number of patients. In CML patients we found a lower relapse incidence and a better RFS in the low dose group (17% vs. 48% and 69% vs. 42%). Most patients with a non-malignant disease received high dose. Survival among non-malignant diseases was 76%. Conclusion. Optimal dose of Thymoglobulin seems to be dependent of diagnose. Patients with acute leukaemia might need a higher dose (6-8 mg/kg) than CML patients (4 mg/kg).

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OUTCOME OF HEMATOPOIETIC PROGENITOR CELLS TRANSPLANT IN PATIENTS WITH ACUTE MYELOGENOUS LEUKEMIA IN FIRST COMPLETE REMISSION REPORT FORM A SINGLE INSTITUTION

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We analyzed 73 consecutive patients during June 1991 to June 2002 with acute myelogenous leukemia (AML) who underwent hematopoietic progenitor cells trans- planta tion (PCT) in 1st complete remission.Adult pts received induction chemotherapy with Citarabine-Mitoxantrone (7/3), 1 or 2 cycles and a BFM-AML regimen in children, all pts received consolidation with Citarabine 12 gr/m2 + Mitoxantrone 24 mg/m2 x 1-4 courses followed by G-CSF 5ug/Kg SC daily.The ablative regimens were busulfan and cyclophosphamide (52 pts) and with etoposide (21 pts).The median age was 35 years old (2-65), and 12 pts(16%) were <15 years old; 33(45%) were females. Distribution within the FAB classification was as follows: M0:7 pts(10%), M1:8 pts(11%), M2:19 pts(26%), M3:3 pts(4%), M4:25 pts(34%), M5:6 pts (9%), M6:1 pts(1%), Biphenotypic:4 pts(5%).The median of WBC at diagnosis was 10.0x109/l (1.0-690.0), only 4 pts had >100.000 x 109/l.According to the cytoge- netics studies at time of diagnosis, the risk groups were:favorable 5 pts (7%), intermediate 22 pts(30%), unfavorable 20 pts (28%), not evaluable 9 pts(12%) and not done in 17 pts(23%).Two courses of induction were needed to achieved CR in 10 pts(14%); 30% received 2 or + courses of consolidation therapy before autograft. Sixty two pts received peripheral blood progenitor cells (PBPC) and 11pts PBPC + bone marrow.The median time to achieved ANC >1.0x109/l was 12 days (8-54); 80% of the pts recovered >25.0 x109/l platelets counts in a median time of 30 days (8-364).Treatment related mortality (TRM) was 8%(6 pts). Thirty five out of 73 pts (47%) were alive and in continous complete remission for a median of 83 months (1-130).The probabilities of event free survival and overall sur- vival at 5 years were 47 and 54% respectively. Younger pts <=50 years old (53 pts) had a better outcome than >50 years old (20 pts)(EFS=59% vs 18%, p <0.001; OS=65% vs 20%, p< 0.001). No statistical differences in event free survival and overall survival was observed according to WBC at diagnosis, FAB clasification, cytogenetic prognostic group, number of induction or consolidation cycles. In summary, our retrospective non randomized analysis shows that 47% of selected adult pts with AML in 1CR can obtain a long-term benefit with high dose chemotherapy and autologous PCT.

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LOW TOXICITY AND EFFICACY OF ^{153}-SAMARIUM-EDTMP/MELPHALAN AS A CONDITIONING REGIMEN FOR SECONDARY ACUTE MYELOGENOUS LEUKEMIA

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With the use of more intensive and effective chemotherapy, radiation, and the improvement in cancer supportive care, many children with malignancies become long-term survivors. Following therapy there is a low risk of myelodysplastic syndrome and secondary AML that are often resistant to conventional therapy including bone marrow transplantation. We report the successful use of a novel preparative regimen in a patient with secondary AML. This regimen uses ^{153}-Samarium ethylenediaminetetramethylenephosphonate (^{153}-Sm-EDTMP) to provide marrow irradiation with an estimated 4000 cGy to the red marrow. This same preparative regimen has been used in multiple myeloma at Mayo Clinic. A 15 year old female developed secondary AML 4 years after completion of therapy for metastatic Ewing's sarcoma (EWS). Patient was treated with combination chemotherapy of alternating cycles of vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide. Peripheral blood progenitor stem cells were collected after the second cycle of chemotherapy with future plans of consolidation with high dose chemotherapy and autologous stem cell rescue, however, due to patient's excellent response to chemotherapy and surgery, therapy was completed without the need of high dose chemotherapy. She received a total lung radiation dose of 1200 cGy. Four years following completion of therapy for EWS, she developed pancytopenia. Bone marrow examination confirmed the diagnosis of AML with monosomy 7. Chemotherapy (high dose cytosine arabinoside and L-asparaginase) was administered resulting in morphologic and cytogenetic remission. No HLA-matched related donor was available for a bone marrow transplant. High dose samarium (day -14; dose 30 mCi/kg ^{153}-Sm-EDTMP) and melphalan (day -2; dose 140 mg/m^2) were chosen as conditioning regimen to avoid potential lung complications due to previous lung radiation. A total of 6.1 x 10 e8/kg mononuclear cells were infused on day 0. Patient achieved engrafment day +40 (no colony stimulating factors were given). She has excellent performance status and no apparent post-transplant complications. At 18 months post-autologous stem cell transplant, she continues in complete remission. ^{153}-Sm-EDTMP and melphalan is a novel, well tolerated regimen and worthy of further study in acute leukemia.

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AUTOLOGUS STEM CELL TRANSPLANTATION AS POSTREMISSION THERAPY FOR ACUTE MYELOID LEUKAEMIA

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Autologus stem cell transplantation can be employed as a postremission therapy in AML but its role remains controversial. Between 1990 and 2001 27 AML pts, without an HLA-identical sibling donor, were autografted at our Division of Hematology using unpurged haematopoietic stem cells. Pts were considered as having a high-risk (HR) disease if they present at least one of the following: secondary AML, unfavourable karyotype, resistant disease to first course of CHT. All the others were considered standard risk (SR) pts. Hematopoietic stem cells source was bone marrow in 25 pts and peripheral blood in 2. At the time of ASCT all

pts were in CR. Conditioning regimen:busulfan and cyclophosphamide. Engraftment was observed in all cases; no TRM was recorded. As by august 2002, 16 (59%) pts are alive in continuos CR at a median follow-up from transplant of 86 months (range 10-148) while 11 (41%) relapsed at a median time from transplant of 13 months (range 6-21). Of these, 4 (36.5%) are alive in 2CR after salvage therapy and 7 (63.5%) died for disease progression. The probability of OS and DFS of the whole population were 67 % and 56% at a median time from transplant of 46 (21-168) and 21 (6-148) months respectively. There was a statistically significant difference in OS (P 0, 0018) and DFS (P 0, 019) comparing HR and SR AML pts in favour of SR group. With the limitation of the small pt number, none of the other analyzed factors (sex, age, MNC dose, interval between diagnosis and transplantation) was found to influence the OS and DFS. Our report confirms that ASCT could improve the outcome of SR AML pts while less favourable results were obtained in HR AML pts. What clearly emerges is the importance of stratifying pts according to prognostic factors in order to employ the appropriate risk-adapted therapeutic approaches. This would suggest that, pts with HR AML and a suitable related or unrelated donor, should be allo-transplanted as soon as possible after the achievement of CR; in such HR cases, however, ASCT could be used if no other alternative treatments are available. We also think that for older IIR pts or for HR AML pts without a donor, investigational approaches (antibody-targeted therapy, other new drugs, leukaemia vaccines, reduced-intensity conditioning regimens, aploidentical allogeneic transplant) should be strongly pursued.