LEUKEMIA

140

SAFETY, TOLERABILITY AND DRUG INTERACTIONS OF ADJUVANT IMATINIB MESYLATE (GLEEVEC®) WITHIN THE FIRST 100 DAYS FOLLOWING STEM CELL TRANSPLANTATION (SCT) IN PATIENTS WITH PH+ CML AND PH+ ALL AT HIGH RISK FOR RECURRENCE

Sheth, S.R.; Hicks, K.; Ippoliti, C.; Giralt, S.; Champlin, R.E.; Anderlini, P. University of Texas M.D.Anderson Cancer Center, Department of Blood and Marrow Transplantation, Houston, TX.

A study (chart review) was conducted to evaluate the tolerability and toxicity of imatinib when used within the first 100 days following SCT in patients without evidence of active disease but at high risk for recurrence. Data collected included assessment of patient tolerance to imatinib dose escalation, maximum tolerated dosage, influence of imatinib administration on tacrolimus serum concentrations, and hematologic and non-hematologic toxicities related to imatinib use in SCT recipients. SCT patients (n=15; M/F 12/3) ranging in age from 16-69 years (mean = 42 years) received imatinib as adjuvant therapy following SCT during the period 5/2001-6/2002. Disease states included Ph+ CML (n=8), Ph+ ALL (n=6) and Ph+ AML (n=1). Stem cell source included peripheral blood in 9/15 patients (60%), and bone marrow (n=6). 9/15 patients (60%) received their SCT from an HLA matched sibling, 3/15 (20%) from a matched unrelated donor, 2/15 (12.4%) from a 1-antigen mismatched related donor, and 1 patient received autologous SCT. Median day of imatinib initiation was day +34 after SCT (range 16-37). Initial imatinib doses ranged from 100 to 400 mg/day. The average daily dose was 100 mg/day. Doses exceeding 200 mg/day were associated with myelosuppression, which required both imatinib dose reduction and initiation of transfusion and growth factor support measures to achieve graft recovery. At all doses, imatinib was associated with reversible hematological toxicity, with Grade 3 and 4 neutropenia observed in 40% and 27% of patients respectively. Significant thrombocytopenia was also noted; with Grade 3 and 4 toxicity observed in 27% and 20% of all patients evaluated. Non-hematologic toxicities were uncommon; with periorbital edema/weight gain and transient elevation in total bilirubin (1.0 mg/dl to 2.3 mg/dl) noted in 1 patient each (6.7%). Administration of imatinib was found to predictably increase tacrolimus serum levels by 25-33% within 72 hours of medication initiation. Empiric tacrolimus dose reduction of 25% prevented further serum concentration fluctuations. These preliminary observations suggest that imatinib can be safely administered within the first 100 days s/p SCT, although the tolerated doses are usually lower than in non-SCT patients.

141

AN INTENT TO TREAT ANALYSIS OF CHEMOTHERAPY VERSUS ALLOGENEIC BONE MARROW TRANSPLANT IN FIRST COMPLETE REMISSION (CR1) FOR ADULT PATIENTS BELOW THE AGE 55 YEARS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): RESULTS FROM PRINCESS MARGARET HOSPITAL

Gupta, V.[1]; Yi, Q.[2]; Minden, M.D.[1]; Lipton, J.H.[1]; Brandwein, J.[1]; Daly, A.[1]; Wells, R.A.[1]; Schuh, A.[1]; Kiss, T.[1]; Messner, H.[1] 1. Leukemia and transplant Program, Dept. of Medical Oncology and Hematology, Princess Margaret Hospital, Toronto, ON, Canada; 2. Dept. of Biostatistics, Princess Margaret Hospital, Toronto, ON, Canada.

The role of alloBMT for adults with ALL in CR1 is disputed. At our center, treatment policy is to offer these patients (pts) alloBMT in CR1 up to the age of 55 years (yrs) if a related donor (either fully matched or one antigen mismatched) is available. In addition, unrelated donor transplants (UD) are offered to Philadelphia positive (Ph+) ALL pts in CR1. Pts without a donor are treated with intensification and maintenance chemotherapy (CT) for 2 yrs. This retrospective analysis was done to evaluate the efficacy of this treatment policy. From 09/92 to 10/01, 97 new pts between the ages 16 to 55 yrs with the diagnosis of ALL (mature B-ALL and acute biphenotypic leukemia pts excluded) were seen at PMH. Five pts (3 treated with palliative CT due to co-morbid conditions, 1 incomplete follow-up & 1 Jehovah's witness) were excluded from this analysis. Of the evaluable 92 pts, 87 (94%) acheived CR1 and included individuals with standard risk, n=30; high-risk, n=46; risk not assessable, n=11. High-risk was defined as presence of one of the following features: WBC >30x10^9/L for B-lineage and >100x10^9/L for T-lineage, time to CR>5 weeks, cytogenetics abnormalities as Ph+ or t (4; 11). 49 pts had a donor (36 HLA identical, 4 one antigen mismatched, 1 haplo-identical and 8 UD) and were designated as alloBMT arm. In the alloBMT arm, 43 pts received transplants (35 in CR1, 7 in CR2, 1 aplastic phase of salvage CT). Of the 43 pts on the CT arm, 6 pts received a rescue transplant in CR2 from UD. Median age in the CT and alloBMT arm was 25 and 34 yrs (p0.21) respectively. Median time to transplant was 189 and 375 days for pts transplanted in CR1 and CR2 respectively. In an intent to treat analysis, a non-significant trend towards better 3 yr. disease-free survival (DFS) was seen in the alloBMT arm (53% vs. 40%, p 0.29). When these results were analyzed according to risk stratification, a benefit of alloBMT was seen only in high-risk group respect to DFS in favor of alloBMT arm (54% vs. 25%, p0.05). Given the limitation of a small sample size, it seems reasonable to recommend alloBMT for high-risk ALL pts in CR1. Further data are needed to decide the utility of this approach in standard risk pts.

Patients acheving CR1	alloBMT arm 3 yr. DFS % (95% C.I.)	CT arm 3 yr. DFS% (95% C.I.)	p (log-rank)
Whole group (n=87)	53 (36-70)	40 (23-57)	NS
Standard risk (n=30)	59 (30-87)	57 (28-87)	NS
High risk(n=46)	54 (31-76)	25 (14-46)	0.05
Risk not evaluable (n=11)	44 (1-88)	40 (0-83)	NS

142

SUCCESSFUL ALLOGENEIC HSCT FOR CONSOLIDATION IN YOUNG CHILDREN WITH HIGH-RISK 11Q23+ ALL IN CR1

Quinones, R.R.[1]; Hunger, S.P.[1]; Gore, L.[1]; Garcea, R.L.[1]; Garrington, T.P.[1]; Foreman, N.K.[1]; Malcolm, J.[2]; Hild, E.[2]; Schissel, D.[2]; Giller, R.H.[1] 1. The Children's Hospital, Denver, CO; 2. University of Colorado Health Sciences Center, Denver, CO.

Nine very young children, ages 2-16 months, with pre-B ALL containing rearrangements of the MLL gene at 11q23 underwent myeloablative allogeneic HSCT in CR1 from either HLA matched siblings (MS: n=2) or unrelated cord blood donors (UCB: n=7). MLL abnormalities included t(4:11) in 3; t(10:11) in 1; t(11:19) in 4 and 11q23 to an unknown partner in 1. All were CD10 negative and 6 of 9 had WBC>50, 000. All patients achieved CR1 following >4 drug induction, aggressive multi-agent consolidation (including B43-PAP monoclonal antibody in 3), and then proceeded to transplant 3 to 4 months after diagnosis. Myeloablative conditioning was identical in all patients with fractionated TBI (1200 cGy with lung shielding at 900 cGy), Cytarabine (83 mg/kg x 6 doses), and Cyclophosphamide (45 mg/kg x 2 doses). UCB recipients also received ATG and Methylprednisolone (MPred). GVHD prophylaxis was with Methotrexate and Cyclosporine A for the MS or CSA/MPred for the UCB recipients. Acute GVHD developed in both MS patients (grade 2 skin) and 1 UCB recipient (grade 3 GI). Chronic GVHD did not occur in either MS recipient and only 1 UCB recipient (extensive). Leukemia-free survival is 87.5% with a median follow-up of 749 days (range 60 to 2025 days). To date, the most frequent toxicity has been endocrinopathies (growth hormone deficiency and subclinical hypothyroidism). All patients have a Lansky Performance Score of 80-100% and impairments of neuro-cognitive function have been only mild and transient. These observations demonstrate that high-risk 11q23+ ALL in young children is curable with myeloablative stem cell transplant. These data prompt the questions whether similar results could be achieved without TBI and whether there is a GVL effect that could be examined using a non-myeloablative approach to potentially reduce toxicity.