*Chinese Journal of Cancer Research 9(1):36-40,1997.*

**Clinical Observations**

# A CLINICAL STUDY OF THE HEMATOPOIETIC STEM CELL TRANSPLANTATION IN 112 PATIENTS WITH LEUKEMIA AND OTHER MALIGNANT DISEASES

Liu Haichuan 刘海川　Yao Shangqian 姚善谦　Lou Fangding 楼方定
Peng Juyun 彭橘云　Wang Lianyuan 王连元　Zhou Qi 周绮
Zhu Jun 朱军　Yan Ying 阎影　Meng Fanyi 孟凡义
Liu Zuobin 刘作斌　Liu Jinghan 刘景汉　Zhang Bolong 张伯龙

*General Hospital of PLA, Beijing 100853*

**One hundred and twelve patients received hematopoietic stem cell transplantation (HSCT), including 91 patients with acute leukemia, 12 patients with chronic myeloid leukemia, 7 patients with lymphoma and 2 patients with myeloma and neuroblastoma respectively. Among them, 14 patients were treated with unpurged autologous bone marrow transplantation (ABMT), 25 patients with purged autologous bone marrow transplantation (PABMT), 40 patients with autologous peripheral blood hematopoietic stem cell transplantation (APBHSCT), 24 patients with allogeneic bone marrow transplantation (Allo-BMT), 9 patients with fetal liver hematopoietic stem cell transplantation (FLHSCT). The three year disease free survival (DFS) rates in these five groups were 68.3%, 67.5%, 69.54%, 57.12% and 33.33% respectively. The relapse rates were 30.76%, 26.80%, 20.8%, 13% and 62.5% respectively. In contrast, in the conventional chemotherapy group, the three year DFS rate and relapse rate were 7.38% and 76.4% respectively. These results indicated that the APBHSCT group had a quicker hematopoietic reconstitution with less complication of infection. All of these five transplantation groups had much higher three years disease free survival rates than that of the conventional chemotherapy group.**

Accepted February 1, 1997

**Key words: Leukemia, HSCT, ABMT, PABMT, FLHSCT, Allo-BMT.**

Hematopoietic stem cell transplantation (HSCT) has been making remarkable progress in recent years and has become an important measure for the treatment of leukemia and some other malignancies. From 1983 to October, 1995, 112 cases of leukemia and other malignancies were treated with HSCT in our hospital, which is reported as follows.

## MATERIALS AND METHODS

### Patients

One hundred and twelve cases were all inpatients, including 58 cases with acute myeloid leukemia (AML), 33 cases with acute lymphoblastic leukemia (ALL), 12 cases with chronic myelogenous leukemia (CML) and 7 cases with malignant lymphoma (ML) and 2 cases with multiple myeloma (MM) and neuroblastoma (NB) respectively. The diagnoses were made by the study of clinical manifestation, blood smear examination, bone marrow

smear examination or histological biopsy.

**Groups of Patients**

In autologous bone marrow transplantation (ABMT) group, there were total 14 cases, with 8 males and 6 females, the median age was 27 (range 11–35)years. 10 cases were AML, 4 were ALL, 12 cases were in the first complete remission (CR1), 2 cases in the second complete remission (CR2), the median interval between remission and ABMT was 7 (range 2–19) months. In purged autologous bone marrow transplantation (PABMT) group there were 25 cases, with 15 males and 10 females, the median age was 29 (range 10–43) years, 17 cases were AML, 6 were ALL, 2 were CML, 20 cases were in CR1, 5 in CR2, the median interval between CR and PABMT was 6.5 (range 3–14) months. In autologous peripheral blood hematopoietic stem cell transplantation (APBHSCT ) group, there were 40 cases, with 25 males and 15 females, the median age was 26.3 (range 3.5–47) years, 18 cases were AML, 13 ALL, 7 ML and 1 MM and NB respectively, 25 cases were in CR1, 11 CR2, 2 CR3, the other 1 case with MM and 1 case with NB were both in non-remission. The median interval between CR and APBHSCT was 7 (range 2–12) months. In allogeneic bone marrow transplantation (Allo-BMT) group, there were 24 cases, with 18 males and 6 females, the median age was 25 (range 14–35) years, 9 cases were AML, 5 ALL, 10 CML, 20 cases were in CR1, 3 CR2, 1 CR3, the median interval between CR and APBHSCT was 5 (range 3–18) months, 23 cases had HLA matched donors, 1 had HLA mismatched donor, 7 cases had ABO incompatible donors. In fetal liver hematopoietic stem cell transplantation (FLHSCT) group, there were 9 cases, with 6 males and 3 females, the median age was 14 (range 6–24) years, 6 cases were AML, 3 ALL, 7 cases were in CR1, 2 cases in CR2 and CR3 respectively, the median interval between CR and FLHSCT was 4 (range 1–8) months. In the conventional chemotherapy group, there were 34 cases, which had rather similar features to the cases of above groups in types of leukemia, age, induction chemotherapy and consolidation chemotherapy, with at least 2 courses of consolidation chemotherapy after CR.

**Methods**

As previously reported,[1-3] in PABMT group, human fetal liver low molecular tumor inhibitor was used for purging in 13 cases, liquid long term culture in 8 cases, hematoporphyrin (PSD-007) with light exposure in 4 cases. In Allo-BMT group, short term methotrexate (MTX) plus cyclosporine A (CsA) were routinely administered for the prophylaxis of graft versus host disease (GVHD). In ABMT group, CsA 1.5–3 mg/kg was administered from day 0 to day 28 for the induction of GVHD. Conditioning regimens were nearly the same in all transplantation groups, which consisted of single or fractionated (2–3 fractions) total body irradiation (TBI) 5–9.9 Gy with the dose rate of 4.5–6.5 cGY/min, and chemotherapeutic agents: Cyclophosphamide (CTX) 50–60 mg/kg/day×2 days intravenously, in addition, Cytosine arabinoside (Ara-c) 500–1000 mg/day×2 days intravenously, Daunorubicin (DNR) 40–60 mg/day×2 days intravenously or Etoposide (Vp16) 150–200 mg/day×2 days intravenously were also added. The median number of mononucleated cell (MNC) and GM-CFU infused were $1.48\times10^8$/kg (range: 0.83–$2.90\times10^8$/kg) and $4.3\times10^4$/kg (range 0.65–$9.3\times10^4$/kg) respectively in ABMT group, $1.32\times10^8$/kg (0.60–$2.70\times10^8$/kg) and $2.92\times10^4$/kg (0.41–$8.65\times10^4$/kg) in PABMT group, $1.8\times10^8$/kg (0.50–$4.98\times10^8$/kg) and $4.7\times10^4$/kg (0.41–$22.8\times10^4$/kg) in APBHSCT group, $3.03\times10^8$/kg (1.45–$3.92\times10^8$/kg) and $7.5\times10^4$/kg (5.04–$32.0\times10^4$/kg) in Allo-BMT group. The number of MNC was $3.60\times10^8$/kg (range 2.60–$14.8\times10^8$/kg) in FLHSCT group. There were no more chemotherapy after transplantation in all groups.

## RESULTS

**Hematopoietic Reconstitution**

The patients in APBHSCT group had faster hematopoietic reconstitution than those in ABMT, PABMT and FLHSCT group, the recovery of bone marrow function and GM-CSF were significantly quicker statistically in APBHSCT group than in the other 3 groups ($P<0.01$) either were white cell count and platelet count ($P<0.05$), while there was no significant difference either between APBHSCT group and Allo-BMT group or between ABMT group and PABMT group in above aspects (Table 1).

**Long Term Effectiveness**

Three years disease free survival (DFS) rate and relapse rate are shown in Table 2.

**The Factors Related to Effectiveness**

The type of leukemia: In ABMT group, PABMT group and APBHSCT group, there were 45 AML cases and 24 ALL cases totally. Their 3 years DFS rate were 74.35% and 56.25% respectively.

The stage of disease before transplantation: 57 CR1 cases and 20 CR2 or CR3 cases had their 3 years disease free survival rates of 78.35% and 57.82% respectively.

The interval between CR and transplantation: The cases with the interval of >7 months and those with the interval of <7 months had their 3 years disease free survival rates of 76.42% and 56.87% respectively. In Allo-BMT and FLHSCT groups, although these 3 factors seem to make some senses, they actually did not statistically.

*Table 1. Median days of hematopoietic reconstitution in transplantation groups*

| | Median days (range) | | | | |
|---|---|---|---|---|---|
| | ABMT group group | PABMT group | APBHSCT group | Allo-BMT group | FLHSCT |
| WBC ($\times 10^9$/L) >1.0 | 28 (19–96) | 26 (16–42) | 20 (14–35) | 21 (15–42) | 35 (30–42) |
| plt ($\times 10^9$/L) >20 | 25 (15–46) | 27.5 (14–96) | 21 (14–64) | 24 (15–35) | 33 (30–150) |
| Cellular of bone marrow | 60 (18–137) | 58 (19–180) | 34.5 (18–90) | 39.5 (19–134) | 53.4 (40–70) |
| Recovery of GM-CFU | 44 (18–133) | 58 (19–180) | 42 (19–426) | 42 (19–426) | 64 (17–365 ) |

*Table 2. Survival rates and relapse rates in 1, 2, 3 years for different groups (Kaplan-Merier plot)*

| Group | No. of cases | Survival rates in 1, 2, 3 years (%) | | | Relapse rate (%) |
|---|---|---|---|---|---|
| | | 1 | 2 | 3 | |
| ABMT | 12 | 82.71 | 69.42 | 68.32 | 30.76 |
| PABMT | 22 | 90.33 | 69.79 | 67.57 | 26.80 |
| APBHSCT | 35 | 90.13 | 69.54 | 69.54 | 20.08 |
| Allo-BMT | 23 | 80.70 | 66.66 | 57.12 | 13.00 |
| FLHSCT | 8 | 64.44 | 44.44 | 33.33 | 62.50 |
| Chemotherapy | 34 | 60.83 | 22.15 | 7.38 | 76.40 |

**Major Complications**

Morbidity of severe infection was 19.4%, consisting of bacteria infection (9.7%), fungi infection (9.7%), 80% of bacteria septicemia were gram-negative bacillus septicemia, while 62.5% of bacteria septicemia were caused by pseudomonas aeruginosa. The total cure rate was 70%, while the cure rate of fungi septicemia was 50%. The morbidity of severe infection in ABMT, PABMT and APBHSCT groups were 18.6%, 16.6% and 11.4% respectively. The total mortality of above 3 groups was 9.5%. The morbidity of severe infection in Allo-BMT group and FLHSCT group were 21.7% and 22.22% respectively, leading to the corresponding mortality of 20.5% and 22.5% respectively, which were remarkably higher than those in the other 3 autologous hematopoietic stem cell transplantation groups. The other complications: There were interstitial pneumonitis (3 cases), hemorrhagic cystitis (15.5%), venooclusive disease (1 case), type B hepatitis (2 cases), tuberculosis (2 cases), graft versus host disease (60.8%) including 85% of mild and moderate grade graft versus host disease, cerebral hemorrhage (1 case),

pulmonary hemorrhage (1 case), and gastro- intestinal bleeding (1 case).

## DISCUSSION

### Hematopoietic Reconstitution

International Bone Marrow Transplantation Registry (IBMTR) and European Bone Marrow Transplantation Group have demonstrated that the patients in APBHSCT group had faster hematopoietic reconstitution and lower morbidity of severe infection than those in ABMT group.[4,5] Antonio et al. showed that for hematopoietic reconstitution in APBHSCT, ABMT and Allo-BMT group, it takes 11, 16 and 15 days to reach WBC>$1.0\times10^9$/L, and 16, 24 and 18 days to reach platelet count>$20\times10^9$/L respectively. Among these 3 groups, the patients in APBHSCT groups had the fastest hematopietic reconstitution.[6] In this study, for APBHSCT, PABMT, ABMT, Allo-BMT and FLHSCT groups, it takes 20, 28, 26, 21 and 35 days to reach WBC>$1.0\times10^9$/L, 21, 25, 27, 24 and 33 days to reach platelet count>$20\times10^9$/L, and 34.5, 60, 58, 39.5 and 53 days to restore a cellular marrow. These results were compatible with those previously published. Among these 5 groups, the patients in APBHSCT group had the fastest hematopoietic reconstitution. The results also showed that the patients in these 3 autologous hematopoietic stem cell transplantation groups had lower morbidity of severe infection than those in the other 2 allogeneic hematopoietic stem cell transplantation groups.

### Long Term Effectiveness

It has been indicated that the long term effectiveness in treatment of leukemia and the other malignancies by means of ABMT and APBHSCT is nearly equal to that by means of Allo-BMT. Therefore, ABMT and APBHSCT are going progressively to replace the role of Allo-BMT. According to the analysis made by IBMTR,[4,5] the 4 years DFS rates of AML and ALL patients in CR1 treated by Allo-BMT were 51±4% and 50±5%, while those in CR2 were 33±3% and 31±7% respectively. It was showed by Carella et al.[7] that for AML patients in CR1 treated with Allo-BMT or ABMT, the relapse rates were 29% and 43%, the mortality were 24% and 10.9% respectively, which showed that the former is much higher than the latter. The 8 years DFS rates were 52% and 49%, which indicated that the long term effectiveness in these 2 groups was quite similar. This study showed that 3 years DFS rates in PABMT, ABMT, APBHSCT and Allo-BMT groups were 68.32%, 67.57%, 69.54% and 57.12%, which were all quite similar. These results were also quite compatible with those reported in foreign publications. The 3 years DFS rate in FLHSCT group was 33.33%, which was superior to that in corresponding chemotherapy group. It had been reported that the 3 years DFS rate of leukemia treated with chemotherapy was 20%–30%. This study showed that the effectiveness of PABMT, ABMT, APBHSCT and Allo-BMT in the treatment of leukemia was superior to that of chemotherapy alone. This result was compatible with those reported in foreign publications.[6,8,9]

### The Prognostic Factors

It was reported that the prognosis of AML was superior to ALL. The patients who had short interval between diagnosis and CR had better effectiveness of treatment. The patients in CR1 had better effectiveness of treatment than those in CR2 or CR3. The patients with >6 months interval between CR and transplantation had better effectiveness of treatment than those <3 months. Conditioning regiments, the consolidation therapy prior to transplantation and purging techniques also had prognostic importance. In this study, the better prognosis of the patients in those 3 autologous hematopoietic stem cell transplantation groups could be related to the following factors: 1. the type of leukemia: In this study, in ABMT, PABMT and APBHSCT groups, there were total 45 cases of AML and 24 cases of ALL whose 3 years DSF rates were 74.35% and 56.25% respectively; 2. The condition before transplantation: 76.8% of total transplanted patients were in CR1, whose 3 years DFS rate was 70.1%, while those in CR2 or CR3 had 3 years DFS rate of 51.7%; 3. The 3 years DFS rate of the patients whose interval between CR and transplantation was >7 months or <7 months were 75.7% and 55.4% respectively; 4. Severe complications and the mortality of transplant related toxicity: in this study, the morbidity of severe infection in Allo-BMT and FLHSCT groups were 21.7% and 22.2%. The mortality related were 20.5% and 22.2%, which were remarkably higher than the mortality of 9.5% in those 3 autologous hematopoietic stem cell transplantation

groups. Therefore, the effectiveness of treatment in ABMT, PABMT and APBHSCT groups were rather good, and were quite similar to that in Allo-BMT group. These results were compatible with those previously published by other authors.[10]

## REFERENCES


1. 刘海川, 姚善谦, 彭橘云, 等. 自体外周血干细胞治疗白血病六例疗效分析. 中华内科杂志 1990; 29:733.
2. 刘海川, 姚善谦, 彭橘云, 等. 自体造血干细胞移植治疗白血病及其他恶性肿瘤 41 例临床研究. 中华内科杂志 1993; 32:461.
3. 刘海川, 姚善谦, 彭橘云, 等. 自体骨髓移植治疗白血病 6 例. 中华血液学杂志 1990; 11:649.
4. Bortin MM, Horowitz MM, Rimm AA, et al. Progress report from the international bone marrow transplant registry. BMT 1992; 10:113.
5. Labopin M, Gorin NC. Autologous bone marrow transplantation in 2502 patients with acute leukemia in Europe a retrospective study. Leukemia 1992; 6(Suppl 4):95.
6. Antonio D, Lacone A, Dragani A, et al. Faster bemopoietic reconstitution after transplantation. 1990; 5(Suppl 1):77.
7. Carella AM, Frassioni F, Van Lint MT, et al. Autologous and allogenetic bone marrow transplantation in acute myeloid leukemia in first complete remission an update of the Genoa experience with 159 patients. Amm Hematol 1992; 64:128.
8. Korbling TM, Fliedner R, Holle S, et al. Autologous blood stem cell (ABSCT) versus purged bone marrow transplantation (PABMT) in standard risk AML influence of source and cell composition of the autograft on hemapoietic reconstitution on disease free survival. Bone Marrow Transplantation 1991; 7:343.
9. Liberti G, Pearce R, Taghipour G, et al. Comparison of peripheral blood stem cell and autologous bone marrow transplantation for lymphoma patients a case-controlled of the EBMT registry data lymphoma working party of the EBMT. Ann Oncol 1994; 5(Suppl 2):151.
10. Juttner CA, To BL, Roberts MM, et al. Comparison of hematological recovery toxicity and supportive care of autologous PBSC autologous BM and allogeneic BM transplants. International J Cell Cloning 1992; 10(Suppl 1):160.