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Chapter 11

Tumorablative Allogeneic Hematopoietic Stem Cell Transplantation in the Treatment of High-Risk and Refractory Leukemia — New Concepts and Clinical Practice

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Additional information is available at the end of the chapter

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1. Introduction

The substance of bone marrow transplantation is the organ transplantation. Accurately, it is the grafting of hematopoietic and immunologic system. Comparing to the transplantation of solid organ, in the hematopoietic stem cell transplantation (HSCT), the ill organ, id est. hematopoietic and immunology system, is ablated by high-dose chemotherapy and total body irradiation(TBI) (conditioning regime). Thus, the normal hematopoietic stem cells could be engrafted and normal function of hematopoietic and immune system could be reconstituted. The standard myeloablative conditioning regimen would be reasonable or enough for the non-malignances of marrow, which needed by replacing therapy, such as marrow failure. However, for treatment of hematopoietic malignances, it maybe not cure the malignance diseases to ablate the normal hematopoietic, immune system and reconstitute the normal function of allogeneic hematopoietic and immune system of patients. Because the leukemic stem cells (LSC) are not only existence in the bone marrow, it might be occurrence in any site of body. For instance, the traditional myeloablative conditioning regimen to treat leukemia could have striking killing effects of leukemic cells, and residual leukemic cells further eradicated by effect of the graft versus leukemia (GVL), but the malignant cells are not always removed at all in the all patients, therefore, relapse post transplantation could be occurred in the some patients. In fact, the traditional allogeneic myeloablative HSCT could cure or improve outcome of acute leukemic patients with standard risk, however, the disease relapse after transplant for acute leukemia with high risk and refractory is 40% to 80% [1-4]. Moreover, the leukemic cells in the majority of relapsed cases originate from inceptive

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leukemic cells at initial diagnosis [5-7], which strongly indicated that the standard myeloablative conditioning regimen could remove the normal lymphohematopoietic system of the recipients and make grafts successfully ecize and proliferate, but could not always kill the residual leukemic stem cells in vivo, particularly the those in extramedullary sites. Those residual leukemic stem cells are the crime for the disease recurrence. We pioneered the tumorablative allogeneic hematopoietic stem cell transplantation (TAHSCT) for treatment of those patients with high-risk, refractory, even advanced-stage acute leukemia. The TAHSCT involve all parts in procedure of transplantation, the principal contents include two elements that are using the individual tumorablative conditioning regimen and enhancing the immunotherapy post-transplantation.

2. Indication of TAHSCT

The indication of TAHSCT is the patients with high-risk, relapsed, refractory, even advanced leukemia. On the one hand, the recurrence of disease post-transplantation in these patients is very high by standard myeloablative transplantation. In the recent years, with the development of immunosuppressant, antibiotic agents and effective supportive therapy, it makes significant improvement to reduce the morbidity and mortality of non-relapse, such as GVHD, infections and multiple organ failure, post allogeneic HSCT, how to prevention and treatment of relapse after allogeneic HSCT in these acute leukemia is the key point to increase the long-term survival. In a recent retrospective cohort from the Center for International Blood and Marrow Transplant Research, the 3-year overall survival rate only was 16% in patients who underwent allo-HSCT in relapse or primary induction failure of acute lymphoblastic leukemia (ALL) [4], for acute non-lymphoblastic leukemia (ANLL) with High-risk, refractory and relapsed, it could be up to 20%-40%. On the other hand, we are faced with more and more of those patients in the clinical transplantation. It is necessary to improve and optimize traditional procedure of HSCT.

3. Rationale of TAHSCT

The leukemia is the malignant clone disease derived from hematopoietic cell. The leukemic stem cell is quite different from the normal hematopoietic stem cell in the biocharacteristics [8]. Comparing to the latter, the former has strong growth vigor and tolerance in some degree to chemotherapy or radiotherapy. Furthermore, the leukemic stem cell is not only in marrow, but also infiltrates to any sites or organs besides hematopoietic system, including some sites in which the anti-leukemia drugs could but achieved to the treating concentration, such as central nerve system, skin and lung and so on. On account of the insight in bionomics of leukemic stem cell, and the results in clinical transplantation, it is demonstrated that standard myeloablative HSCT could not enough to root out of leukemic or leukemic stem cells, particularly the in extramedullary sites. Therefore, the myeloablative HSCT is not equal to TAHSCT, the residual leukemic or leukemic stem cell is the convict for relapse [9].

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Although GVL effect after transplantation produces a marked effect, it is always later after transplant. Eventually, the residual leukemic stem cell could be proliferation and disease relapse occurrences [10].

The purpose of tumorablative tailored conditioning regimen is not only to suppress or destroy the immune and hematopoietic system to make space for engraftment, but also to ablate leukemic stem cell, especially the leukemic stem cells in the "asylum" of extramedullary sites, and to induce or enhance the GVL effect as far as possible [11].

Compared with myeloablative transplantation, besides removal of normal hematopoietic tissue, TAHSCT focuses more on killing residual tumor cells, especially elimination of extramedullary residual tumor cells. In the selection of drugs, it puts more emphasis on the killing intensity of drugs on leukemic cells, the maintenance effective concentration and enough time of killing effect, and reduction of post-transplant leukemia relapse to minimum [11]. Compared with non-myeloablative transplantation or reduced toxicity transplantation, the latter still retains hematopoietic stem cells of recipient, in some extent, for autologous hematopoietic reconstruction, but also residue a certain amount of leukemic stem cells which might cause relapse, therefore the reconstructed mixed hematopoietic chimerism often requires donor lymphocyte infusion (DLI) to ensure the possibility of a successful engraftment, and the prevention and treatment of relapse are also dependent on DLI and subsequent immunotherapy or targeted therapy[11]. Their comparison is showed in Figure 1.

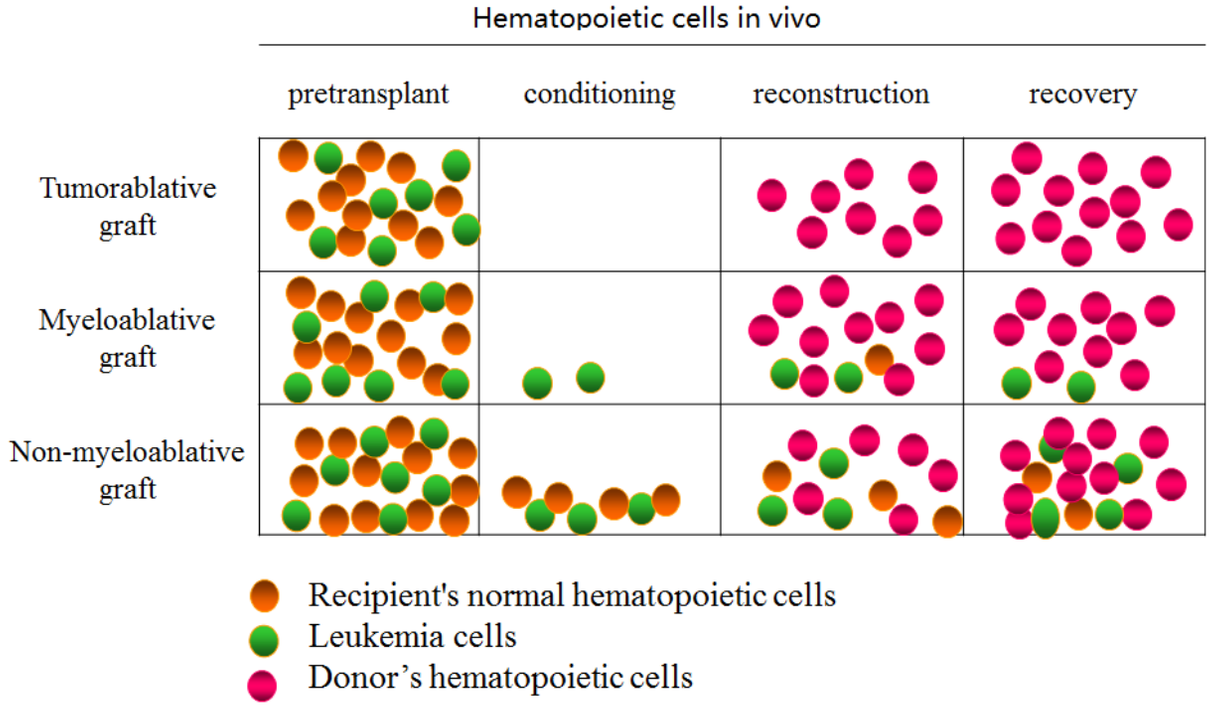


Figure 1. Comparison of tumorablative to myeloablative and non-myeloablative transplantation

4. Strategy for TAHSCT

Based on the regularity and characteristics of disease relapse after transplantation, we proposed a preventive pathway for leukemic recurrence post-transplantation in the early of 2007 years [12]. They are general prophylaxis, early intervention and clinical therapy. The general prophylaxis means to avoid the selection of high risks (shown in table 1) during the grafting procedure, the key points in early intervention are to institute a reasonable individual tumorablative conditioning regimen. The clinical therapy is to treat the leukemia in the early or frank relapse, including immunotherapy post transplantation. In the clinical practice for 5 years, the relapse rate of 85 and 83 cases with high risk, refractory or relapse received TAHSCT in 2008 and 2009 year was 2.3% and 5%, respectively [11]. It was strikingly advance; however, the challenge is still presence. Obviously, among the risks associated to relapse, the conditioning regimen and immunotherapy are more important.

Elements	High risk for relapse	Low risk for relapse
Recipient		
tumor cell burden	high	low
extramedullary disease	yes	no
unfavorable chromosome	Yes	no
unfavorable molecule	yes	no
sensitive to chemotherapy	insensitive	sensitive
performance status	worse	good
GVHD post grafting	no	yes
Grafts		
peripheral stem cell vs marrow cell	low	high
number of grating cells	low	high
T cell depleted	yes	no
Grafting technique		
conditioning regimen	non myeloablative	myeloablative
GVHD Prophylaxis	strong	fairly
immunosuppressive agent		reduce or stop early
interfere by immunotherapy		yes

Table 1. The risks associated to relapse in the transplantation

5. Approach to tumorablative conditioning regimen

Theoretically, the tumorablative conditioning regimen should contain drugs or TBI to ablate normal hematopoietic and immunologic tissue, also drugs or agents to get rid of leukemic or leukemic stem cell, particularly, those in the extramedullary sites. The ideal drugs should be high effective and targeted on the leukemic or leukemic stem cell, however, these special target agents have not been successfully used in clinical, and it should be exploited in the

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future. According to the clinical experiences for successful treatment of refractory or relapsed leukemia, and combining with standard myeloablative regimen, we selected some regimen with high effective and less toxicity, and establish a tumorablative conditioning regimens (shown in table 2).

Regimen	content	indication
HDAra-C+Bu/Cy	Ara-C 2.5g/m^2 IV, -11d- -9d Bu 1mg/kg.6hrs, -8d- -6d MCCNU 250mg/ m^2 (ANLL) or Vm26 300mg/ m^2 (ALL), -5d CY 50mg/kg.d IV, -3- -4d rest, -2 - -1d, HSCT d 0	High risk in CR
G-CSF primed HDAra-C+Bu/Cy	G-CSF 5μg/kg.d sc, -12- -9d Ara-C 3 g/ m^2 IV, -11d- -9d Bu 1mg/kg.6hrs, -8d- -6d MCCNU 250mg/ m^2 (ANLL) or Vm26 300mg/ m^2 (ALL), -5d CY 50mg/kg.d IV, -3- -4d Rest, -2 - -1d, HSCT d 0	Remission or early relapse in high risk patients with bone marrow hypoplasia or leukopenia
FLAG/RIT	G-CSF 5μg/kg.d sc, -14- -9d Ara-C 2 g/ m^2.d CI, -13- -9d FDL 30mg/ m^2.d IV, -13 --9d BSF 0.8mg/kg.6hr IV, -8 - -6d CY 50 mg/m^2.d IV, -5 - -4d MCCNU 250mg/m^2.d, -3d Rest, -2 - -1d, HSCT d 0	Progressive or advanced patients with ANLL
TBI/FLAG/CY	TBI 1.5 - 2 Gy, Bid, -13- -11d Vm26 300 mg/m ^{2}. IV, -10d G-CSF 5μg/kg.d sc, -10- -5d Ara-C 2 g/ m^2.d CI, -9- -5d FDL 30mg/ m^2.d, IV, -9 --5d CY 30 mg/kg.d IV, -4 - -3d Rest, -2 - -1d, HSCT d 0	Progressive or advanced patients with ALL

* All regimens can be used in transplantation of HLA matched unrelated and halo-identical HSCT, but ATG must be added. ATG, antithymocyte globulin; Ara-C, cytarabine; Bu, busulfan; BSF, busulfex; Vm26, teniposide; CY, cyclophosphamide; FDL, fludarabine; MCCNU, semustine; RIT, reduced intensive transplantation; TBI, total body irradiation.

Table 2. Some tumorablative conditioning regimen*

FLAG/reduced intensive transplantation (FLAG/RIT regimen) A large number of clinical practice confirmed that intravenous infusion of high-dose cytosine (Ara-C) was an effective rescue measure for the treatment of refractory or relapsed leukemia, about 40% refractory acute myeloid leukemia (AML) could achieve remission. Pharmacokinetic study on high-dose Ara-C intravenous infusion revealed that intravenous infusion of Ara-C (1.8-32.0) g/m^2 for 2 hours, every 12 hours, the plasma concentrations could reach (8-24) μg/ml, cerebrospinal fluid concentrations was about (10-15)% of plasma concentration. This high concentration of this drug in blood and cerebrospinal fluid was thought to be the pharmacological basis of significantly increased efficacy [13-15]. Ara-C combined with anthracycline (uniquinone) or acridines drugs could further improve the CR rate to 50 % [16, 17].

FLAG protocol consisting of fludarabine combined with Ara-C plus recombinant human granulocyte-stimulating factor (G-CSF) is currently a potent and well-tolerated treatment for refractory and relapsed AML. Fludarabine is a nucleotide analogue, acts as a ribonucleic acid inhibitor by phosphorylation to active triphosphate form F-ara-ATP. As a substrate for DNA synthesis in leukemic cells, F-ara-ATP has anti-leukemia activity by inhibition of DNA polymerase and ribose reductase, especially has a strong effect on quiescent cells. In vitro and in vivo studies proved that addition of fludarabine before Ara-C administration might increase the intracellular concentration of Ara-CTP, enhance the cytotoxicity and clinical efficacy of Ara-C, so that the CR rate of refractory and relapsed AML reaching 50% - 75%, CR period reaching 9 months and above [18]. Schmid et al [19] used combination chemotherapy with fludarabine and Ara-C for 4 days followed by reduced-toxicity allogeneic hematopoietic cell transplantation and post-transplant donor lymphocyte infusion in 103 refractory acute myeloid leukemia patients, followed up for a median period of 25 months. It was found that 1, 2 and 4-year overall survival rates were 54%, 40% and 32%, respectively. Therefore, the FLAG/RIT regimen is mainly used in treatment of ANLL with progressive or advanced patients with ANLL.

TBI/FLAG/CY regimen It consists of total body irradiation, FLAG and reduced cyclophosphamide, and always utilized to treat ALL in progressive or advanced phase. Because, TBI was more effectiveness in allo-HSCT for ALL.

G-CST priming regimen It is usually to treat the ANLL at remission or early relapse in high risk with bone marrow hypoplasia or leucopenia. Granulocyte-stimulating factor can induce the proliferation of AML cells and increase the proportion of S phase cells in vitro or in vivo, thereby enhancing cell sensitivity to chemotherapeutic drugs. Reasonable and sequential application of G-CSF and chemotherapeutics is another effective option for the treatment of refractory AML, such as the above-mentioned FLAG protocol and CAG protocol composed of low-dose Ara-C (LD-Ara-C), aclacinomycin and G-CSF. In fact a large number of experimental and clinical studies confirmed that pre-transplant application of G-CSF not only promoted the differentiation of T cells to TH2 and enhanced the function of regulatory T cells, but also amplified immature antigen-presenting cells and plasmacytoid dendritic cells, which was beneficial for maintenance of post-transplant T cells function and reduction the incidence of GVHD. Morris ES, et al. also confirmed that through modification of pegylation and combination with Flt-3L, G-CS might lead to activation and amplification of donor in-

http://dx.doi.org/10.5772/53031

variant NKT (iNKT) cells, a marked increase of post-transplant cell mediated $CD8^+$ T cytotoxicity, and enhancement of GVL effect [20]. Takahashi et al. had proved that application of G-CS together with conditioning regimen could reduce the post-transplantation relapse in refractory myeloid leukemia [21]. Ooi et al. used G-CSF + Ara-C or + total body irradiation and fludarabine as a conditioning regimen, and performed unrelated cord blood transplantation in adult AML patients, the results showed that 2-year disease-free survival was 76%[22]. Rational application of G-CSF in tumorablative conditioning regimen not only augmented anti-leukemia effect, but also separated GVHD and GVL effect to a certain degree, improved the safety of transplantation and reduced the relapse [23].

Regimen containing high Ara-C For the transplantation of ANLL with high risk in the complete remission, we used the regimen containing high Ara-C as tumorablative conditioning. As early as 2004, Lu DP et al. reported the application of GIAC protocol (Ara-C, busulfan, cyclophosphamide, MCCNU and G-CSF activated bone marrow and peripheral blood) including high-dose Ara-C, MCCNU and G-CSF for mobility of peripheral blood stem cells in donor-recipients HLA-unmatched or haploidentical hematopoietic stem cell transplantation. Post-transplant observation confirmed this protocol resulted in a higher disease-free survival rate (70%) and lower relapse rate (13%), further suggesting the necessity of intensified measures with direct anti-leukemic cell effects in the conditioning regimen [24].

Based on the above theory and the specific situation of individual patient, we have modified GIAC protocol and designed the HDAra-C+Bu/Cy. Preliminary clinical attempts have yielded encouraging results (Table 2).

In clinical practice, about one-third of AML and more than half of ALL patients relapsed firstly manifested as extramedullary relapse, such as leukemic sarcoma or infiltration into the central nervous system. So that, drugs with good liposolubility and ability to penetrate blood-brain barrier, such as Carmustine (BCNU), methyl cyclohexyl nitrosourea (MCCNU), teniposide (VM26) as well as high-dose Ara-C or MTX, should be chosen as a part of tumorablative regimen.

Our tumorablative conditioning regimen possess following features: The first, it could enhance the intensity of anti-leukemia chemotherapy. All regimens included continuous infusion of medium dose Ara-C for 72 hours, meanwhile drugs with good liposolubility were added such as MCCNU (acute myeloid leukemia) and teniposide (acute lymphocyte leukemia). The duration of the regimen extended to 11-14 days, which not only enhanced the anti-leukemia effects on leukemic (stem) cells in hematopoietic tissue, but also ensured a longer maintaining period of effective drug concentration in extramedullary tissue including central nervous system, and further depletion of leukemic (stem) cells in all tissues. Secondly, granulocyte-stimulating factor was added in some regimes. It not only recruited quiescent leukemic (stem) cells into proliferation cycle, increased the sensitivity to the killing effects of drugs, but also reduced or alleviates the incidence of post-transplant GVHD through regulation of immune cells, or might induce GVL effects. Third, the reduction of the dosage of alkylating agent decreased or alleviated the toxic and side effects, under the circumstances of depletion of normal hematopoietic tissue and effective immunosuppressant. Fourth, individualization was emphasized. In clinical, application of these regimens should focus on in-

dividualization, in view of the differences of cytogenetics and gene alterations in the pathogenesis of leukemic cell, clinical manifestations and prognosis, or pre-transplant disease, performance status and drug tolerance of patients. In addition, the regimens should also be adjusted in accordance with the donor source, for example, the transplantation of unrelated or haploididential donor, anti-lymphocyte globulin (ATG) should be included in the corresponding conditioning regimen [25]. We met a case of AML-M5 with primary resistance to chemotherapy, the blasts remain more than 50% in marrow after induction by daunomycin plus Ara-C (DA), idarubicin plus Ara-C (IA), mitoxantrone plus Ara-C and etoposide (MAE), CAG and FLAG regimen, but, after AE (amsacrine + Vm26) regimen, near CR was achieved. Then he received haplo-identical transplantation using TBI/FLAG/CY regimen in February, 2012, in which amsacrine + Vm26 instead of FLAG, because his leukemic cell is sensitive to amsacrine and Vm26. After successful engraftment, he is still alive in continual CR up to now.

6. Detection of minimal residual disease and immunotherapy post TAHSCT

Detection of minimal residual disease (MRD) and immunotherapy post transplantation are very impotent principle in the TAHSCT [25]. Although it is almost specific method to detect the marrow morphology, clone culture, immunophenotype, and abnormal gene or protein of leukemic cell, clinically, the flow cytometry (FCM) and polymerase chain reaction (PCR) are the more convenience, fast and sensitive. It should be routinely done post transplantation. In some patients, relapse proceeded in extramedullary sites, even sarcoma, especially, CNS, subperiosteum, skin, serous cavity, lung and intestinal tract, so image analysis also is necessity, such as, CT, MIR, PET or PET-CT. We had used a PET-CT to detect proceed relapse in extramedullary sites in an advanced case with ANLL after underwent unrelated HSCT, and successful pinpoint treated by the cyberknife.

With regard to immunotherapy, firstly, immunosuppressive agents should be decreased or even stopped as quickly as possible, when GVHD was strictly controlled. Then, if necessary, some immune modulators should be given, such as interferon, IL2 and thymopeptides. For the two latter, which should not use in T cell malignances. Finally, it is the cell therapy [25, 26].

Donor lymphocyte or G-CSF mobilized peripheral blood stem cell infusion (DLI/DSI) for treatment of leukemia relapse after allo-HSCT was introduced in early 1990s, being extremely effective in chronic myeloid leukemia. The DLI for AML relapse post-transplant has been questioned in general. Recently, Schmid C, et al retrospectively analyzed the data of 399 patients with AML in first hematological relapse after HSCT whose treatment did or did not include DLI. After correction for imbalances and established risk factors, the two groups were compared with respect to overall survival. Further, a detailed analysis of risk factors for survival among DLI recipients was performed. The results confirm a role for an allogeneic GVL effect in AML [27]. Various modifications of DLI have been investigated. These included the systematical use of mobilized donor PBSC concentrates instead of lymphocytes,

http://dx.doi.org/10.5772/53031

or the systemic application of cytokine induced killer cells (CIK) for additional immunostimulation to increase GVL efficacy. In addition, infusion of allogeneic natural killer (NK) cells is also a promising innovative immunotherapy, being alloreactive NK cells reported to produce a strong GVL effect after haploidentical HSCT in patients with advanced AML, without causing GVHD [28]. In vitro studies have suggested the possibility to create specific antileukemic cytotoxicity by stimulation of donor lymphocytes using AML-derived dendritic cells. Porter and colleagues reported encouraging results from a phase I trial using conventional DLI, followed by an additional infusion of ex vivo activated donor T cells. Therefore, we used DLC, DSI or CIK as maintenance therapy after HSCT for patients in remission or in a minimal residual disease situation in our program to exploit the GVL efficacy, and got a ducky result. Recently, we treated 18 cases in relapse after allogeneic HSCT, including 11 of HLA matched sibling, 5 of haploidentical and 2 of matched unrelated donor by donor's dendritic cell-primed CIK (DC-CIK). After the median number of 3.6 X 10^9 DC-CIK infused, molecule complete remission was obtained in 12 cases (68%), and 11 of 12 cases are survival with a median follow-up of 12 (range 6-41) months, except 1 died of treatment related complication. It confirms that donor derived DC-CIK infusion is efficacious and safety in this setting [29]. However, DLI or CIK infusion was often associated with a considerable risk of GVHD, and clinically, we should be careful to assay and prevent from GVHD.

Along with screening and identification of new immunogenic tumor protein or peptides, anti-tumor specific functional T cells could be produced in vitro, the anti-leukemia specific immunotherapy would have more definite position in treatment of relapse post transplantation. Further experimental and clinical research are required to overcome the obviously high burden of leukemia blasts to escape from an allogeneic immunereaction in relapsing patients after allogeneic HSCT for refractory acute leukemia.

7. Clinical practice of TAHSCT

In fact, the first TAHSCT with HLA identical donor we preformed was in 2007 for a 54 years old female with resistant relapse, She was diagnosed as AML in July 2004 and obtained CR after 3 courses of chemotherapy by daunomycin plus Ara-C (DA), idarubicin plus Ara-C (IA) and mitoxantrone plus Ara-C (MA), and then received 13 courses of intensive consolidation chemotherapy including high dose of Ara-C, and autologous CIK infusion for 3 times. Her leukemia relapsed in the end of Dec 2006, and could not response to the several courses of reinduction chemotherapy. Before she received tumorablative allo-HSCT, there were 27% of leukemic blasts in marrow. The FLAG/RIT regimen was conditioned for HLA-identical sibling HSCT on February 22nd 2007. Her neutrophil and platelet were successfully engraftment on +18 days, chimerism analyses shown that full donor chimerism achieved by +30 days. Assay of MRD periodically by FCM monitoring after TAHSCT was zero. Grade I aGVHD of intestinal tract and liver was happened on +51 days, and thereafter invasive fungal infections in sinusitis, lung, liver on right-sidedness (pathological culture supported mucor infection) were happened, The Aspergillus was detected in sputum culture. All the

complications above were controlled and cured after symptomatic treatment. She is still alive in continue complete remission up to now (more than 78 months).

The first TAHSCT with haploidentical donor we did was in 2008. The case with 22 years old male was diagnosed as AML with t (8; 21), AML1/ETO positive in August 2005. He had received several courses of intensive consolidation, and maintenance chemotherapy including high dose Ara-C. Three years later, he had leukemia relapse, and not obtained CR again after reinduction chemotherapy. Before transplantation, there were 75% of leukemic blasts in marrow. The patient received the FLAG/RIC/ATG conditioning regimen for HLA haploidentical TAHSCT from his sibling. On January 1st 2008, after TAHSCT, engraftment was durable with full donor chimerism, and detection of non MDR by FCM, chromosome, and realtime PCR for AML1/ETO fused gene monitoring. Limited cGVHD was controlled by CSA and prednisone in fewer months. The patient is still alive in disease-free survival (DFS) until now.

Between August 2006 and march 2007, a total of 57 patients with high risk/refractory leukemia were received tumorablative individualized conditioning regiments, included HDAra-C +Bu/Cy, G-CSF primed HDAra-C+Bu/Cy, and FLAG/RIT. Among 57, 20 patients of acute lymphoblast leukemia (ALL), 23 patients of acute myelogenous leukemia (AML), and 12 patients of chronic myeloid leukemia (CML) in accelerate or blast crises phase, and 2 patients of myelodysplastic syndrome–refractory anemia with excess of blasts (MDS-RAEB). 28 patients received haplo-identical transplantation, 17 patients HLA-identical unrelated donor transplantation and 12 patients HLA-identical sibling transplantation. The results showed that 56 patients, but one recovered with autologous hematopoiesis, attained durable engraftment. The median time to an absolute neutrophil count >0.5x10^9/L was 16 (range: 12-21) days. The median time to a platelet count >20x10^9/L was 18 (range: 12–32) days..With a median follow-up of 17.5 (2-34)months, the probabilities of OS and DFS were (74.7±6.1) % and (62.4±6.7) %, respectively. The incidence rate of aGVHD in grades II-IV and III-IV were (19.3±5.2)% and (12.3±4.3)% respectively. Extensive chronic GVHD was observed in 36 (64.3%) patients. Cytomegaloviremia (CMV) was observed in 39 (68.42%) patients. Hemorrhagic cystitis was observed in 13 (22.8%) patients. Fungous and bacterial infection occurred in 16 (28.07%) and 38 (66.67%) patients, respectively. The relapse in all patients occurred in 14 (24.6%). Among them, relapse rate in high risk and advanced group (blast cells were more than 20% in bone marrow) were 28.1% and 15.6%, respectively. 11 of 14 patients relapsed in marrow, 3 of 14 relapsed in extramedullary sites, 15 patients died (6 from hematological relapse, 5 from infection of bacterial and fungous, 4 from chronic GVHD) after 100 days. The toxicity in this TAHSCT could be tolerance, and overcame [30,31].

Recently, we reported forty-nine patients, from first affiliated hospital, Chinese PLA General Hospital, of hematological malignancy with high risk or refractory, including 24 AML, 14 ALL, 9 non-Hodgkin lymphoma (NHL), and 2 CML in blast crisis. All patients received haploidentical TAHSCT, in which umbilical cord mesenchymal stem cells were added. All patients achieved engraftment and complete remission after TAHSCT. Regimen-related toxicities were tolerable. Only five patients (10.2%) experienced relapse at a median time of 192 days after transplantation. The probability of 2 year leukemia free survival (LFS) in

http://dx.doi.org/10.5772/53031

AML and CML patients was 83.3%, which was significant higher than that in the ALL and NHL patients (40.0%, P<0.05) [32]. Our another 45 patients, form Beijing Dao-pei hospital, with refractory recurrent AML treated by TAHSCT [33]. The median blasts in marrow were 36% (20% to 92%) before transplantation, including 6 of HLA identical sibling, 9 of unrelated and 30 of haploindentical transplantation. All but 2 patients attained durable engraftment. The incidence of grade II to IV aGVHD and cGVHD were 34% and 59.1%, respectively. With median follow-up 30 (0.5 to 57) months, the relapse rate was 29.2%. Twenty nine (60.2%) patients remained CR since transplantation. Three years DFS and Overall survival (OS) were 60.2% and 62.6%, respectively. These data confirmed that the individualized tumorablative allogeneic hematopoietic stem cell transplantation is a promising and safety choice for treatment of high risk, refractory or relapse leukemia, even with high leukemia burden.

In the recent, these TAHSCT have being carried out in many hospitals in China. A total of 250 patients from 5 hospitals enrolled, the all patients with high-risk, resistant or relapse, even advanced hematological malignances, including leukemia and lymphoma [32,33-34]. The primary clinical observation revealed that the results are the similar to that above (data not published). Obviously, its efficacy must be confirmed by randomized, prospective clinical trials on a large population.

Actually, many investigators have being devoted to prevent from and treat recurrence post transplantation in refractory leukemia, including Schmid C, et al, who used a sequential treatment with chemotherapy and reduced-intensity conditioning for allogenic stem cell transplantation [19], and Takahashi S. et al, which used GCS-F combined regimen for allogeneic bone marrow transplantation shown above [21]. Recently, Eom KS, et al. reported that FLANG salvage chemotherapy as a safe bridge to transplantation for patients with relapsed or refractory acute myeloid leukemia is an effective regimen [35]. Arita K, et al. described that a sequential chemotherapy and myeloablative allogeneic hematopoietic stem cell transplantation for refractory acute lymphoblastic leukemia [36], and so on. All of them have obtained encouraging results. Comparing to them, our TAHSCT strategy emphasizes more entirety, individual and tumorablative efficacy in the sitting of tolerated toxicity.

8. Conclusion

In summary, the TAHSCT strategy is a primary entirety approach for treatment of hematopoietic malignances with high-risk, refractory or resistant relapse, based on the successful experiences either standard HSCT or chemotherapy for these patients. It is true, there were still some relapse post TAHSCT strategy, however, and it has reduced the relapse rate to about 20% in these patients, so it also highlights the need to improve. Theoretically, the residual leukemic stem cell is the chief offender in relapse post transplantation. We can utilize the differences in the biocharacteristics between normal and leukemic stem cells, which result of regulating disorder in proliferation, differentiation, apoptosis and ecize, signaling pathways, and so on [8,37,38], to exploit the targeted drugs with specific killing effects on LSC and niches for LSC, apoptosis-promoting and differentiation-inducing effects, such as

tyrosine kinase inhibitor, FLT3 inhibitor [39], hypomethylating agent, and so on, together with the specific functional T cell adoptive immunotherapy. It should provide a broad prospect for the prevention and radical cure of relapse after TAHSCT in patients with refractory and relapsed leukemia.

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