Clinical Case Reports

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CASE REPORT

Fludarabine, idarubicin, and cytarabine regimen together with TKI followed by haploidentical hematopoietic stem cell transplantation, a success for relapsed Ph+ acute lymphoblastic leukemia

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Funding Information
No sources of funding were declared for this study.

Received: 5 February 2015; Revised: 7 July 2015; Accepted: 7 October 2015

***Clinical Case Reports* 2016; 4(4): 390–395**

doi: 10.1002/ccr3.438

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Key Clinical Message

In this report, a case of relapsed Ph+ ALL was remedied by reinduction, and consolidation regimen of TKI and Flu+ Ara-C+ IDA (FLAI) combination, followed by haploidentical SCT. Results suggest that FLAI together with TKI and subsequently with haploidentical SCT could be applied for relapsed Ph+ ALL.

Keywords

Allogeneic hematopoietic stem cell transplantation, graft-versus-host disease, Ph+ acute lymphoblastic leukemia, T cells.

Introduction

Acute lymphoblastic leukemia (ALL) is a heterogeneous malignant clonal hematological disease. Combined chemotherapy for adult ALL can achieve a high remission rate similar to that for the pediatric ALL [1, 2]. For Philadelphia chromosome-positive (Ph+) ALL, the combination of chemotherapy and tyrosine kinase (TKI) therapy enhanced the rate of complete remission (CR) and prolonged the CR time, but failed to extend the overall survival (OS) [3]. Relapse after chemotherapy plus transplantation is the main cause of death in adult ALL patients [4]. The risk classification of ALL reflects the disease's prognosis and guides the treatment of pediatric ALL. The treatment of adult ALL based on the risk classification failed to achieve better therapeutic efficacy, and allogeneic hematopoietic stem cell transplantation (Allo-HSCT) becomes the preferred treatment for adult ALL in the standard-risk group [5]. The relapsed ALL leads to high mortality (~90%) of Ph+ ALL [6]. The current focus of studies includes postrelapse reinduction chemotherapy, intensified treatment after remission, and optimization of allo-HSCT.

The selection of salvage chemotherapy for relapsed adult ALL is highly correlated with the timing of the relapse. For the relapses within 6 months after remission, the original induction chemotherapy can be considered. Alternatively, other programs or clinical trials should be applied [6]. Currently, the regimen using an increased

dose of multidrug chemotherapy combined with targeted therapy is generally adopted. Treatment based on the detection and elimination of minimal residual disease (MRD) is an ideal treatment strategy after remission. Allo-HSCT can effectively eliminate MRD by pretreatment with high-intensity chemotherapy followed by graft-versus-leukemia (GVL) effects. This approach represents the only clinically relevant treatment for the clinical cure of relapsed adult ALL [7].

Here, we report a case of secondary adult Ph+ ALL with osteosarcoma patient who was treated with a novel TKI-based FLAI regimen including TKI, Fludarabine (Flu), Idarubicin (IDA), and Cytarabine (Ara-c) reinduction. After the successful induction of remission, the patient was administered with an incremental dose of FLAI to intensify and consolidate the treatment efficacy. Subsequently, the patient underwent haploidentical allo-HSCT and TKI was stopped after transplantation. During this period, septicemia, fungal infections, and second-degree skin rejection occurred. The post-transplantation MRD was negative. The patient is currently in a hematologic and molecular remission without relapse in leptomeninges or the extramedullary site. Results from this case suggest that the regimen could be an option for the patients with relapsed adult Ph+ ALL.

Diagnosis

A 33-year-old male sought treatment due to knee pain 11 years ago. He was diagnosed as osteosarcoma based on imaging and pathology (Fig. 1). After two cycles of IFO and ADM chemotherapy, the patient underwent a knee replacement surgery followed by 12 cycles of chemotherapy in 2-year duration. Two years ago, the patient was admitted to our hospital due to fever, fatigue, and bleeding gums. Blood test revealed the following: white blood cell (WBC) 131.38×10^9/L, hemoglobin (Hb) 117 g/L, and platelet (Plt) 38×10^9/L. Lymphoblasts represented 90% of the bone marrow. Immune typing revealed the following distribution of markers: CD19 88.84%, CD13 71.51%, CD10 90.99%, CD34 92.34%, TDT 20.58%, cyCD79a 71.65%, and cyCD 22 37.85%. The chromosomal analysis was 46, XY, t (9; 22)[7]/46, idem, i (17q)[1]. The patient was positive for the BCR-ABL (P190) fusion gene. Immunohistochemical examination failed to identify lymphoid antigens in the primary osteosarcoma (data not shown), and the presence of relevant lymphocyte clones was ruled out. The patient was diagnosed as leukemia of secondary Ph+ ALL (B cell).

Our Routine Treatments for ALL

According to our established treatment system, ALL patients are administered remission therapy induced by a regimen of vincristine, daunorubicin, cyclophosphamide, L-asparaginase, and prednisone (VDCLP). After achieving CR, sequential administration of high-dose methotrexate and vincristine + prednisone (HD-MTX+VP) and Hyper-CVAD A/B, in which the combination of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternates with high-dose methotrexate and cytarabine is provided. Allo-HSCT is performed for patients with appropriate available donors and indications (patients younger than 55-years old, with status of completed remission, with proper donor, without organs dysfunction, and severe infections status, and with approval by ethical committee and patient's consent) after pretreatment with improved busulfan/cyclophosphamide (BU/CY). Without appropriate donor available, the patient undergoes autologous hematopoietic stem cell transplantation or is administered with three courses of Hyper-CVAD A/B chemotherapy followed by maintenance treatment with 6-MP combined with MTX. If relapse occurred at any time during this period, the FLAI regimen is administered as reinduction therapy. If remission occurs again, the original program is repeated at a higher dose for consolidation therapy followed by allo-HSCT; if remission does not occur, the transplant program is directly performed (Fig. 2). To prevent central nervous system leukemia, triple intrathecal chemotherapy drugs (MTX+DXM+Ara-c) readministered in combination, twice for each course, at least eight times by lumbar puncture and intrathecal injection. For Ph+ ALL patients, TKI will be administrated immediately after the confirmation of positive Ph chromosome or bcr/abl fusion gene expression till transplantation, but will be suspended if the number of neutrophiles is less than 0.2×10^9/L.

The treatment Process for This Particular Patient

After pretreatment with VP (VCR 1.5 mg/m^2 d1, Pred 60 mg/m^2 d1–7) for 1 week, induction chemotherapy with VDCLP was administered. During the 14-day period, the lymphoblast decreased to 1% of the bone marrow, and CR1 was reached after chemotherapy. After the second round of chemotherapy with HD-MTX+VP (HD-MTX 3 g/m^2 d1, VCR 1.5 mg/m^2 d1, Pred 60 mg/m^2 d1–5), lymphoblast rebounded to 10%. After the third course of chemotherapy with Hyper-CVAD A course (CTX 300 mg/m^2 d1–3, VCR 2 mg d4, d11, Doxorubicin 50 mg/m^2 d4, Dex 40 mg/d d1–4, d11–14), the percentage of lymphoblast in the bone marrow rebounded to 86% with BCR-ABL (P190) at 4.452×10^3, indicating blood and molecular relapse. On the basis of the second-generation TKI nilotinib, the FLAI (Flu 20 mg/m^2 d1–5, IDA 10 mg/m^2 d1–3, Ara-C 1 g/m^2 d1–5) regimen was

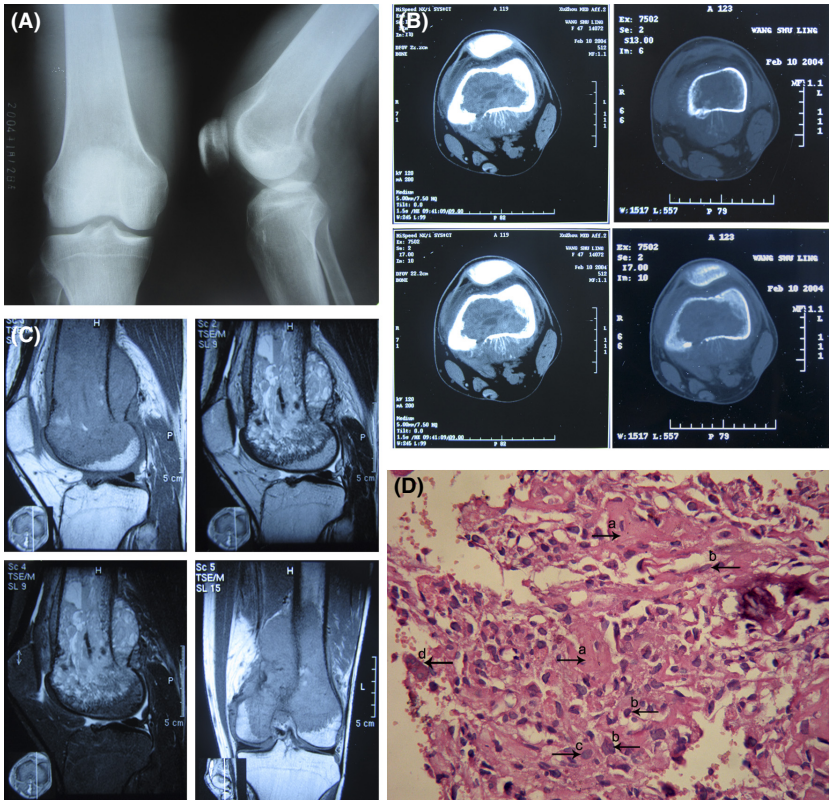

Figure 1. Imaging and pathology diagnosis of osteosarcoma (A, X-ray). The epiphyseal line in right lower femur is fuzzy, and the cortical bone of the posterior is coarse and partially with visible periosteal reaction. (B, CT) The lower part in right femur shows osteolytic destruction, the surrounding shows radiated spicula and soft tissue swelling, and the partial shows visible tumor bone formation. (C, MRI) T1W sagittal and coronal: the lower part of right femur shows flaky uneven long T1 signal intensity, with small patchy short T1 signal intensity inside, and the surrounding shows soft tissue swelling with uneven long T1 signal intensity. T2WI Sagittal: the lower part of right femur shows flaky uneven long T2 signal intensity, with small patchy short and equal T2 signal intensity inside, and the surrounding shows soft tissue swelling with uneven long and equal T2 signal intensity. Fat-suppressed T2WI sagittal: the lower part of right femur shows flaky uneven slightly high signal and high signal intensity, with small patchy short and equal T2 signal intensity inside, and the surrounding shows soft tissue swelling with uneven slightly high and equal T2 signal intensity. (D, Pathology) oncological osteogenesis as shown as pink homogenous strip shape osteoid matrix (a); sarcomatoid-like cells with fusiform, polygonal, round, large nuclei, and hyperchromatic shape alongside the osteogenesis edge (b); prominent nucleoli (c); osteoclast-type multinucleated giant cells (d). HE staining (H&E, hematoxylin and eosin).

administered as reinduction chemotherapy, and hematologic remission as well as complete remission at the genetic and molecular level were achieved (normal chromosomal karyotype, quantitative detection of BCR-ABL (P190) $<1 \times 10^3$). Subsequently, the patient received the intensified treatment with a combination of incremental FLAI (Ara-C 2 g/m^2 d1–5) and TKI. The pretreatment chemotherapy with the improved BU/CY (Hu 40 mg/kg q10 h × 2 −10 d, Ara-c 2.0 g/m^2 −9 d, BU 3.2 mg/kg [−8 d] to [−6 d], CTX 1.8 g/m^2 [−5 d] to [−4 d], Me-CCNU 150 mg/m^2 −3 d, ATG [rabbit] 2.5 mg/kg [−5 d] to [−2 d]) was performed followed by 3/6 matched haploidentical bone marrow transplantation at loci HLA-A, B, and DRB1 which was donated by the patient's father. The number of CD34 + stem cells in the transplantation was 4.49×10^6/kg. aGVHD (acute graft-versus-host disease) was prevented with the combination of CSA, MMF, and MTX. The neutrophil hematopoiesis began to recover within +13 d, and platelet hematopoietic reconstitution was achieved at +12 d. After +16 d, the patient underwent second-degree skin rejection and EB/CMV infections, and got remission after treatment with antiviral and glucocorticoid. At +4 months, the patient experienced fever and cough with fungi detected in the sputum smear and positive GM test, indicating fungal infection. Voriconazole and caspofungin together with intravenous gamma globulin were sequentially administered, and the infection was under control after 5 weeks. Immediately after the transplantation, the patient stopped taking TKI. Cyclophosphamide was administrated for half a year after allo-HSCT. Samples were taken every 3 months and the karyotype and BCR-ABL (P190) fusion gene were

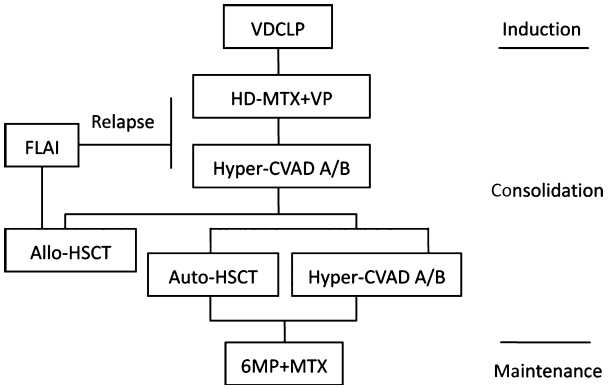

Figure 2. Treatment system for adult acute lymphoblastic leukemia. VDCLP, combination of vincristine, daunorubicin, cyclophosphamide, L-asparaginase, and prednisone; HD-MTX+VP, high-dose methotrexate, vincristine and prednisone; Hyper-CVAD A/B, combination of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternates with high-dose methotrexate and cytarabine; FLAI, combination of Fludarabine, Idarubicin, and Cytarabine; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; Auto-HSCT autologous hematopoietic stem cell transplantation.

monitored after the transplantation. Negative results have been seen so far in the following 23 months without any abnormal clinical symptoms. In addition, the patient was in remission not only in blood and bone marrow, but also in cytogentic and molecular biology level without relapse in leptomeninges, or in an extramedullary site. The STR detection suggests 100% donor chimerism.

Discussion

Allo-HSCT can effectively eliminate MRD by pretreatment of a high-intensity chemotherapy regimen and the GVL effect. This has been proved to be an effective treatment for the clinical cure of hematologic malignancies [8]. In addition, allo-HSCT is the only option for refractory and relapsed adult ALL [4]. How to achieve a second remission for patients with relapsed ALL and how to enhance the GVL effect, and reduce transplant-related complications (transplant-related mortality, TRM, and transplant-related toxicity, TRT) remain the most pressing challenges in the field.

Effective salvage chemotherapy can achieve a second remission in refractory relapsed ALL, providing patients with the option of allo-HSCT. Based on the experience of pediatric chemotherapy, intensified chemotherapy as well as multidrug therapy can improve the efficacy of chemotherapy [9]. Combination therapy with a monoclonal antibody and other targeted drugs can further improve the remission rate [10]. For example, combination of Hyper-CVAD and CD20 monoclonal antibody was effective for B-cell ALL [11], and combination of Hyper-CVAD and TKI was effective for Ph+ ALL [3, 12]. In addition, combination chemotherapy based on nucleoside analogs, such as nelarabine, has recently been applied as chemotherapy for T -cell ALL. Ph+ ALL accounts for approximately 15–30% of ALL cases [13] and the TKI-based combined chemotherapy is currently the main treatment for these patients. For the relapsed Ph+ ALL as reported in this case study, the combination of the nucleoside analogs fludarabine and idarubicin with high-dose cytarabine (FLAI regimen) on the basis of the TKI dasatinib was applied as salvage treatment and resulted in a hematologic and molecular remission. Increased dose of cytarabine in second consolidation chemotherapy further reduced the number of residual leukemic cells. Thus, the patient was able to undergo subsequent transplantation.

Allo-HSCT is the only curative choice for the treatment of adult ALL for its superior anti-leukemia effect. Currently, the most widely accepted approach is allo-HSCT with a completely matched related donor (MRD). It is also possible to perform allo-HSCT with a fully matched unrelated donor (MUD) or allo-HSCT with reduced intensity conditioning (RIC). The latter approach is mostly used in the treatment of elderly ALL and weakens the clearance of the MRD during pretreatment while reducing the toxicity [14]. The largest prospective ECOG/E2993 clinical trial to date also confirmed that allo-SCT achieves better OS than autologous transplantation and intensified consolidation chemotherapy after remission with a lower relapse rate. Especially in the standard-risk group, better OS and disease-free survival (DFS) were observed. In the high-risk group, although OS differed from the standard-risk group due to transplant-related complications, the relapse rate was significantly reduced and a further reduction in the transplant-related toxicity is expected to improve the efficacy of allo-HSCT [5]. Haploidentical transplantation is also a potential transplant model. Xiaojun Huang et al. demonstrated that haploidentical transplantation with a related donor based on the improved and optimized BU/CY pretreatment regimen and GIAC transplant protocol could result in a stronger GVL effect and a lower relapse rate without increasing the TRM and TRT [15–18]. Based on BY/CY, multidrug help to myeloablatively clear MRD, high dose of Ara-c and me-CCNU help to prevent central nervous system invasion because of blood–cerebrospinal fluid barrier penetrability, and ATG does well for prevention of aGVHD. G-CSF mobilized stem cells from peripheral and bone marrow probably help to induce immune tolerance and provide effectively GVL effect. Because no suitable matched donor was available for the patient in this study, a haploidentical allogeneic transplant from his father was implemented. The safety of this transplantation

model was evident. Only a transient septicemia and a controllable second-degree skin aGVHD were observed in the neutropenic period. After the transplantation, the presence of MRD (bcr/abl P190) was not detected even without TKI. Currently, the patient is 27 months post-transplantation. The patient has remained in hematologic and molecular remission. This allogeneic transplant system effectively broke the immune barrier. Furthermore, because of the convenience of more sources of stem cells from related donors as well as the safety of the transplantation process, the stronger GVL effect and the lower relapse rate, the current transplant option with a fully matched related donor will probably not be the first choice.

In this particular case, a TKI-based salvage induction therapy with multidrug treatment was applied. The dose escalation after remission and haploidentical allo-HSCT were conducted to reduce the tumor burden and increasing the GVL effect as much as possible. The treatment successfully saved this patient with secondary refractory and relapsed ALL. The safety of using a TKI-based FLAI regimen followed by haploidentical allo-HSCT has been clearly demonstrated in this case and this provided an additional option for the treatment of refractory and relapsed ALL.

Conflict of Interest

The authors of this manuscript have no conflicts of interest to disclose.

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