Reduced intensity chemotherapy, tyrosine kinase inhibitor, and blinatumomab in a pediatric patient with Philadelphia chromosome-positive ALL and mechanical valves

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Abstract

The outcome of pediatric patients with Philadelphia chromosome (Ph)-positive acute lymphoid leukemia (ALL) has improved with addition of tyrosine kinase inhibitors to an intense chemotherapy. However, it is associated with high incidences of adverse effects and requires new therapeutic strategies for maximum anti-leukemic effect and reduced toxicities. We describe a challenging adolescent case with Ph-positive ALL and mechanical mitral and aortic valves due to Shone's syndrome. The patient received reduced intensity chemotherapy and blinatumomab with dasatinib and is in deep molecular remission. Long-term anticoagulation was achieved with enoxaparin for mechanical valves and unfractionated heparin during procedures.

Introduction

Philadelphia chromosome (Ph)-positive acute lymphoid leukemia (ALL) comprises approximately 2% of pediatric ALL and is associated with a poor outcome [1]. Chromosomal translocation, t(9;22)(q34;q11.2), forms the oncogenic fusion protein, *BCR-ABL1* , which drives leukemogenesis via aberrant tyrosine kinase signaling. Historically, the prognosis of children with Ph-positive ALL who received intensive chemotherapy with or without allogeneic hematopoietic cell transplant (HCT) in first remission was dismal with 5-year overall survival of 30% to 50% [2, 3]. The introduction of tyrosine kinase inhibitor (TKI), imatinib, to intensive chemotherapy backbone resulted in 5-year disease-free survival of 70%, which was comparable to those treated with allogeneic HCT [4]. However, this combination was associated with high incidence of complications such as infection, [4, 5], which necessitates the development of treatment regimens that integrate TKI into a reduced intensity chemotherapy regimen to enhance efficacy while minimizing toxicity. Here, we describe an adolescent patient with Ph-positive ALL and congenital heart disease with prosthetic heart valves necessitating lifelong anti-coagulation who received tailored treatment regimen with reduced intensity chemotherapy, dasatinib, and blinatumomab while using heparin-based anti-coagulation.

Case Description

Thirteen-year-old Caucasian male with histories of mechanical mitral and aortic valve replacements for Shone's syndrome, mild to moderate mitral and aortic valve stenoses and pulmonary hypertension presented with headache for 1-week, anemia, and subtherapeutic anti-coagulation indices. Home medications included furosemide, sildenafil, warfarin, and aspirin with prophylactic enoxaparin added on 2 months prior due to subtherapeutic international normalized ratio (INR).

Complete blood count showed a white blood cell count of 10.8 x 10^9/L with 56% lymphoblasts, hemoglobin of 6.5 g/dL, and platelet count of 188 x 10^9/L. Coagulation studies showed an INR of 1.8 (goal 2.5-3.5), partial thromboplastin time of 20.4 seconds and anti-Xa of 0.28 IU/ml. Bone marrow examination confirmed the diagnosis of B-ALL with ALL-type*BCR-ABL1* fusion identified by RT-PCR and fluorescence in-situ hybridization. Next generation sequencing confirmed *BCR-ABL1* and*RUNX1* S172fs. There was no central nervous system (CNS) involvement. Cardiac echo showed left ventricular ejection fraction of 55% with mean mitral and aortic pressure gradients of 12mmHg and 23 mmHg, respectively.

Induction regimen included prednisone, vincristine, and daunorubicin followed by cyclophosphamide, cytarabine, and mercaptopurine (Figure 1). To avoid increased thrombotic risk, pegaspargase was omitted. Anthracycline was given with cardioprotective agent, dexrazoxane. Therapeutic enoxaparin and aspirin were continued without warfarin. An Ommaya reservoir was placed to administer CNS-directed therapy (methotrexate, hydrocortisone, and cytarabine) to avoid anticoagulation interruption. Dasatinib (80 mg/m^2/day, maximum 140 mg) was initiated on day 5 of induction. The minimal residual disease (MRD) was 4.9% on day 15 and <0.01% at the end of induction by flow cytometry with a detectable *BCR-ABL1* transcript at 1 x 10^{-4}.

The patient developed a subdural hematoma at the Ommaya site while being appropriately anticoagulated prompting switch to intrathecal CNS-directed therapy at the end of induction. To minimize procedure-based anticoagulation interruptions, enoxaparin was bridged to unfractionated heparin, which was stopped 4-6 hours prior to the procedure and restarted 6-12 hours post procedure along with restarting enoxaparin. The patient subsequently received five courses of blinatumomab with daily dasatinib without experiencing cytokine release syndrome or neurotoxicity. *BCR-ABL1* transcript became undetectable after the third cycle. At one-year from diagnosis, the patient developed signs of congestive heart failure (cough, dyspnea, and pitting edema) with bilateral pleural effusions and increased mean aortic valve pressure gradient of 33mmHg on echocardiography. Cardiac catheterization demonstrated normal mobility and appearance of valve leaflets without worsening of mild to moderate atrial and mitral valve stenoses. With diuretic therapy and switching from dasatinib to imatinib (340 mg/m^2/day, maximum 600 mg), the patient's cardiac status stabilized without further complications.

The patient is currently on daily imatinib and a conventional maintenance regimen that consists of monthly cycle of daily mercaptopurine and weekly methotrexate for three weeks interrupted by a week of pulse therapy with vincristine and dexamethasone for three months followed by one-month infusion of blinatumomab for 20 months; he will finish the remaining 10 months of treatment with conventional regimen (Figure 1). CNS-directed treatment consists a total of 20 doses of intrathecal therapy without prophylactic cranial irradiation. The patient has remained in molecular remission for 14 months without thrombotic events.

Discussion

Due to underlying congenital cardiac disorder with mechanical mitral and aortic valves, we tailored a reduced-intensity chemotherapy backbone without asparaginase and initiated dasatinib during induction with incorporation of blinatumomab prior to and during maintenance therapy.

Treatment-related morbidity and mortality in Ph-positive ALL patients are major concerns demonstrated by previously published multi-institutional trials with TKI [4, 6]. Effective reduced intensity chemotherapy is required especially in patients with co-morbidities. Molecular targeting agents and immunotherapy are new treatment strategies for ALL. TKI remarkably improved the outcome of Ph-positive ALL. A recent randomized study showed that pediatric patients who received less intensive chemotherapy with dasatinib (80 mg/m^2/day), a dual ABL/SRC inhibitor with greater activity against *BCR-ABL1* and better CNS penetration than imatinib, had better event-free and overall survival along with superior CNS leukemia control than those treated with imatinib (300 mg/m^2/day) [7]. Adults with Ph-positive ALL had excellent outcome with ponatinib, newer and highly potent TKI against wild-type and mutant *BCR-ABL1* including T315I[8], in combination with reduced intensive therapy. However, pediatric experience is limited and ponatinib is associated with higher incidences of cardiovascular complications than other TKIs.

Blinatumomab is a bispecific T-cell engager antibody largely used in MRD-positive and relapsed/refractory pediatric and adult ALL[9, 10]. A combination of blinatumomab with reduced-intensity chemotherapy and TKI is a successful strategy in adults with Ph-positive ALL [11, 12] . Although blinatumomab is associated with cytokine release syndrome and neurotoxicity, the incidence and degree of such adverse effects can be reduced by decreasing leukemia burden prior to blinatumomab therapy as in our case. Moreover, no significant cardiac or thrombotic events have been reported with this approach.

A unique challenge in our patient was appropriate anticoagulation for mechanical cardiac valves in the setting of increased thrombotic risk with the usual pediatric ALL-directed treatment including asparaginase and dexamethasone [13]. Prior to diagnosis, warfarin achieved optimal anticoagulation without history of adverse bleeding events. Warfarin is the anticoagulant of choice for prosthetic valve thromboprophylaxis. Due to complexity of warfarin management and drug interactions with several chemotherapies through CYP3A4 metabolism, low-molecular weight heparin was used in our case. Furthermore, use of unfractionated heparin bridging reduced the duration of being off anticoagulation making heparin-based therapy the optimal choice to manage mitral and aortic valve associated coagulopathy in our patient during treatment for his leukemia. We considered other anticoagulants, such as direct oral anticoagulants, but these are not recommended in patients with prosthetic valves [14] and are not approved in pediatric patients.

To our knowledge, we describe the first adolescent patient with Ph-positive ALL and mechanical valves treated with reduced intensity chemotherapy, TKI and blinatumomab, in addition to, heparin-based anticoagulation therapy, respectively. This strategy allowed deep molecular remission and facilitated a unique antithrombotic regimen to reduce the cardiac complications. The success of using immunotherapy in combination with less intensive chemotherapy and TKI in the adult setting can serve as a platform on which to pursue innovative cancer treatments that achieve maximum anti-cancer effect while minimizing treatment-related toxicities in pediatric patients.

Conflict of Interest statement

Hiroto Inaba receives research grant from Servier. The other authors have no conflicts to declare.

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Figure Legend:

Figure 1: Schematic representing tailored treatment regimen for Ph+ALL in an adolescent patient with aortic and mitral mechanical valves on chronic anticoagulation. Abbreviations: MHA, methotrexate + hydrocortisone + cytarabine; TKI, tyrosine kinase inhibitor; D, day; IT, intrathecal.