Effective re-induction therapy with dasatinib and clofarabine in relapsed Philadelphia chromosome positive acute lymphoblastic leukemia

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Abstract

This case discusses a 10 year old female patient with a late relapse of Ph+-B-cell precursor acute lymphoblastic leukemias (ALL) who had previously been treated with chemotherapy and allogeneic stem-cell transplantation. Treatment for relapse consisted of single-agent dasatinib, followed by 2 blocks of a combination of dasatinib and clofarabine as consolidation therapy. Using this schedule both morphological and cytogenetic complete remission were obtained. This regimen was well tolerated, and no major toxicity concerns occurred. Subsequently, the patient received a 2nd stem cell transplantation from a matched unrelated donor. Unfortunately, the child died after complete molecular remission at day +104 post-transplantation, due to a disseminated adenoviral infection. We conclude that dasatinib and clofarabine combination therapy was safe and effective in this patient, and should be further explored as a salvage regimen in relapsed/refractory Philadelphia chromosome positive ALL patients.

Introduction

Approximately 2-5% of newly diagnosed acute lymphoblastic leukemias (ALL) cases in children are Philadelphia chromosome positive (Ph+) ALL. The Philadelphia chromosome, a fusion of the ABL gene on chromosome 9q34 to the BCR gene on chromosome 22q11, is a well-known poor prognostic factor in both pediatric and adult ALL. In children, overall survival rates with chemotherapy only are in the 30-50% range.2,3 The BCR-ABL fusion gene results in uncontrolled elevated tyrosine kinase activity.4

With the development of the tyrosine kinase inhibitor (TKI) imatinib, which inhibits the down-stream effects of the BCR-ABL fusion gene, outcome may improve.5 Studies in adults may not provide a definite answer for the use of TKIs in children with Ph+ ALL, given the differences in breakpoints in BCR and ABL between children and adults, which are known to result in differences in kinase transforming activity.6,7 Pediatric patients usually carry the minor breakpoint cluster region of BCR (m-bcr or p190), as opposed to adult patients where the breakpoint is usually found in the major breakpoint cluster region (M-bcr or p210). Data found in animal models suggest that the minor breakpoint induces leukemia with a greater transforming potential than the major breakpoint.8 Imatinib activity in newly diagnosed Ph+-ALL was recently demonstrated by the Children’s Oncology Group (protocol AALL0031).9 Their study showed a 3-year event free survival rate of 80% in patients receiving continuous imatinib combined with an intensive chemotherapy regimen, and was superior to treatment without imatinib using historical controls. Even though this was a non-randomized study, the results indicate that treatment for children with Ph+ ALL should probably include a TKI, given that no other studies with chemotherapy alone have ever reached this level of efficacy. Recently, second generation TKIs became available, which are being given in case of imatinib resistance or intolerance due to the greater potency against BCR-ABL, their retained activity in case of imatinib-resistance ABL mutations, their ability to inhibit SRC which may be implied in resistance and, their ability to penetrate into the cerebrospinal fluid as has been shown specifically for dasatinib.10,11 It is known that relapsed/refractory patients with Ph+-ALL may respond to dasatinib, although generally, these responses are not durable,12,13 and hence other therapy-elements need to be added. This case report presents a relapsed Ph+-ALL patient treated by re-induction therapy with single-agent dasatinib, followed by consolidation with clofarabine and dasatinib and subsequent stem-cell transplantation (SCT). We conclude that this treatment schedule may be a successful strategy in relapsed/refractory Ph+-ALL.

Case Report

A 6-year-old girl was diagnosed with Ph+-B-cell precursor (BCP) ALL in November 2003. The karyotype showed the Philadelphia chromosome (molecular evaluation showed that it concerned the minor breakpoint) plus additional abnormalities: 52,XX,+X,+2,+4,t(9;22)(q34;q11),+6,+17,+20[10]/46,XX[10]. She was treated according to the high risk arm of the Dutch Childhood Oncology Group protocol ALL-9.14 First complete remission (CR1) was achieved at the end of induction. However, approximately 2 months after obtaining CR1, 6% blasts were morphologically detected in the bone marrow. Therapy was switched from ALL-9 to the European EsPhALL protocol, which had just opened, and imatinib (300 mg/m2) was added to the chemotherapy regimen. Morphological complete remission was again achieved, and after intensification, she received an allogeneic haplo-identical SCT. Imatinib (300 mg/m2) was electively re-introduced on day +28 post-SCT, and was stopped 1 year later.

Three years after the transplantation, a relapse was diagnosed with 77% blasts in the bone marrow and 2% blasts in the peripheral blood. There was no central nervous system involvement, and white blood cell count was...
6.8x10⁹/L. Minimal residual disease (MRD) analysis was performed using BCR-ABL levels with ABL as a household gene, as described before (Figure 1). MRD results were set to 1.0 (100%) at diagnosis of relapse, and follow-up data were expressed as relative values according to the disease-load at diagnosis of relapse (Table 1). Mutation analysis for ABL resistance mutations was carried out in the sample taken at diagnosis of relapse using direct sequencing, but no resistance mutations were detected.

The patient was referred to our center for inclusion in the CA180018 dasatinib study (protocol CA180018; NCT 00306202), and following the screening period which confirmed eligibility she started treatment with dasatinib orally at 80 mg/m² QD. No organ toxicity occurred during the first dasatinib course. After 3 weeks a re-evaluation was performed (Table 1). The bone marrow morphology showed a decrease of blasts to approximately 18%; however, both flow-cytometry and cytogenetics showed complete remission and MRD levels were decreased to 0.06. At day 42, six weeks following single-agent dasatinib, the same discrepancy was noted, with morphology showing approximately 20% blasts, and flow-cytometry and cytogenetics indicative of complete remission. At this time, MRD levels were increased to 0.12. Because of the uncertainty regarding the achievement of CR, and in-line with the protocol, intra-patient dose-escalation of dasatinib to 100 mg/m² QD was initiated. Three weeks after this dose-increase the response was re-evaluated and now results were indicative of complete morphological and cytogenetic remission, although MRD levels increased. Because the protocol only allowed single-agent treatment with dasatinib, and we wanted to offer further treatment with chemotherapy in preparation for a stem-cell transplant, the patient came off-study.

The patient was then further treated with two blocks of clofarabine consisting of 52 mg/m² IV once daily, for 5 consecutive days. During clofarabine administration no dasatinib was given, but following each course, dasatinib was re-started two days after stopping clofarabine. Dasatinib was then given for 14 days, at a dose of 100 mg/m² QD. Following these two blocks she was in complete morphological and cytogenetic remission. Although MRD levels dropped to 0.013 at day +127 after relapse, she never obtained a major molecular remission (defined as a level of ≤0.001 compared to base-line).18 During clofarabine and dasatinib administration the patient showed only some mild toxicity concerns and was therefore not hospitalized. At day +155 following relapse she was transplanted again, this time with a 9/10 matched unrelated stem cell donor. A reduced intensity conditioning schedule was used, because of the prior total body irradiation during the first transplant procedure. Conditioning consisted of Treosulfan (3x14 gr/m²), Melphalan (2x70 mg/m²) and ATG (total 10 mg/kg). Standard graft versus host disease prophylaxis with ciclosporin A (2 mg/kg IV) and methotrexate (10 mg/m² at day +1, +3 and +6) was given after SCT. Unfortunately, she died in complete molecular remission (no BCR-ABL transcript was detectable at day +31 post 2nd SCT) of a disseminated adenoviral infection at day + 104 post 2nd SCT. Dasatinib was not given after 2nd SCT. Until her death, our patient showed 100% donor chimerism in blood and bone marrow.

Discussion

Despite a major general improve of outcome in pediatric ALL, the prognosis in Ph+ALL patients is less favorable.²,³ So far there has been no comprehensive strategy for relapsed Ph+ALL.

In this patient, our aim was to use dasatinib for remission induction, followed by clofarabine combined with dasatinib for consolidation, and a 2nd SCT, aiming at cure. After 9 weeks of treatment all results pointed towards a complete morphological and cytogenetic remission. To further reduce MRD-levels pre-SCT, we started sequential therapy with clofarabine and dasatinib. After two courses of this therapy our patient underwent SCT. The patient showed a complete molecular remission following SCT, which was not seen before. The potential advantages of single-agent dasatinib as re-induction therapy include that it may be well-tolerated, has less organ-toxicity than regular re-induction schedules, and can be taken at home orally. Our patient experienced all of these benefits. A potential disadvantage may be the risk of developing resistance mutations during this phase of single-agent therapy. Our choice for adding clofarabine was based on the safety and activity profile of clofarabine for relapsed ALL, and its subsequent registration both in Europe and the United States.¹⁹ Moreover, the patient had initially suffered from poor disease control on a regular ALL protocol, hence offering her a relapse protocol with similar medication was considered undesirable.

Current studies suggest that a combination of clofarabine with etoposide and cyclophosphamide is tolerable, although clofarabine is given at lower dose in such combination regimens.²⁰,²¹ However, at time of treatment, these data were not known yet and therefore we used single-agent clofarabine. In our patient, the clofarabine plus dasatinib combination was safe, and not associated with prolonged neutropenia or severe infections. Particularly, no cardiac, hepatic or skin toxicities were mentioned in this child while receiving clofarabine and dasatinib.

Three other pediatric case reports described the use of dasatinib for relapsed Ph+ALL after therapy with imatinib.²²-²⁴ Millot et al.²² showed that a 4-year old child with Ph+ ALL in 1st relapse, after imatinib therapy and an allogeneic haplo-identical SCT, achieved a second complete cytotologic and molecular response, and underwent a 2nd SCT. Their patient was still in complete molecular remission 18 months after the second SCT.²⁵ A case report by Ishida et al.²³ describes a 15-year old girl with Ph+ ALL with an early relapse after the first SCT. She achieved complete molecular remission with dasatinib at 140 mg/day and 12 months after the second SCT she still remains in complete remission.

![Figure 1. Minimal residual disease status versus treatment. Minimal residual disease was calculated using the BCR-ABL/ABL ratio. Results were normalized to base-line levels.](image-url)
in molecular remission. The use of dasatinib in this case was associated with myalgia, nausea, opportunistic infection and gastrointestinal bleeding which were not attributed to the SCT.\textsuperscript{23} De Castro et al.\textsuperscript{24} reported about the use of dasatinib in a multiple relapsed Ph\textsuperscript{+} ALL patient with a history of an allogenic haploidentical SCT. Dasatinib was used here in combination with other agents, such as etoposide, vincristine, prednisone and asparaginase. After this treatment, the patient achieved a bone marrow remission and could undergo a second SCT with the same donor as the first time. Unfortunately, two months after the second SCT the patient had a fourth bone marrow relapse and received palliative care. This child died four months after the second SCT.\textsuperscript{24}

Conclusions

In conclusion, dasatinib could be considered as a useful and tolerable drug for remission induction in heavily pre-treated Ph\textsuperscript{+} ALL children. Following remission induction, clofarabine and sequential dasatinib could be given for consolidation therapy. Unfortunately our patient died in complete molecular CR from an infectious cause. Previous studies showed that adenovirus is a significant cause of morbidity in pediatric allogeneic SCT.\textsuperscript{25,26} It can however not be included that clofarabine, which is known to be very immune-suppressive, also contributed to this. In this case report, we provide evidence that the chosen re-induction regimen was tolerable, and hence its use in children with a good physical condition and able to undergo a second round of intensive therapy, should be explored further in children with refractory Ph\textsuperscript{+} ALL, who are in good physical condition and able to undergo a second round of intensive therapy.

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