Clinical Case Report

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Dasatinib monotherapy for newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia with pulmonary infection in induction remission

A case report and review of the literature

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Abstract

Rationale: There is currently no clinical standard for induction therapy in the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ ALL). Chemotherapy in combination with tyrosine kinase inhibitors (TKIs) recognized as the first line of therapy to induce remission in Ph^+ ALL patients; however, both the infectious and non-infectious toxicities remain high and lead to early excessive treatment-related mortality (TRM). Single-agent TKI "monotherapy" may reduce toxicity and TRM; however, TKI induction monotherapy and its effectiveness in the induction of remission in newly diagnosed Ph^+ ALL has yet to be investigated.

Patient concerns: A 59-year-old man who was newly diagnosed Ph^+ ALL with 93% blast cells and a *t* (9, 22) karyotype. But the patient also suffered from pulmonary infection, including fever and dyspnea.

Diagnoses: The patient was newly diagnosed with Ph^+ ALL with pulmonary infection.

Interventions: The patient received oral dasatinib monotherapy (100 mg qd) for 28 days as induction therapy.

Outcomes: The patient reached complete remission with negative minimal residual disease detected by real-time quantitative polymerase chain reaction after induction therapy for 28 days.

Lessons: This is the first report on the use of dasatinib monotherapy in the absence of other drugs, such as steroids, for induction therapy in a newly diagnosed Ph^+ ALL patient with pulmonary infection.

Abbreviations: allo-HSCT = allogeneic hematopoietic stem cell transplantation, BM = bone marrow, FCM = flow cytometry, HSCT = hematopoietic stem cell transplantation, Hyper-CVAD = cyclophosphamide, vincristine, doxorubicin, and dexamethasone, MRD = minimal residual disease, Ph^+ ALL = Philadelphia chromosome-positive acute lymphoblastic leukemia, RT-qPCR = real-time quantitative polymerase chain reaction, TKIs = tyrosine kinase inhibitors, TRM = treatment related death.

Keywords: chemotherapy, dasatinib, induction therapy, positive acute lymphoblastic leukemia

1. Introduction

There is currently no standard method for induction therapy for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ ALL)—a phenomenon which is underscored by the NCCN guideline's encouragement of clinical trials in Ph^+ ALL induction therapy.[1] The use of tyrosine kinase inhibitors (TKIs) in combination with chemotherapy has achieved positive outcomes in induction therapy for Ph^+ ALL, but the complications of this combination therapy are high.[2] Therefore, the TKIs combined with corticosteroids, rather than chemotherapy, have been investigated as an induction therapy for Ph^+ ALL.[3] However, the use of corticosteroids leads to numerous side effects of varying degree of severity, such as, increased infection, adrenal insufficiency, Cushing syndrome, hypertension and diabetes, some of which may be severe.[4] In the past, the efficacy, safety, and tolerability of single-agent dasatinib was assessed in imatinib-resistant or imatinib-intolerant adult refractory/relapsed Ph^+ ALL patients who underwent prior hematopoietic stem cell transplantation (HSCT), received prior chemotherapy or interferon-α (IFN-α) and previously received imatinib.[5] However, the use of single-agent TKIs as a monotherapy as induction remission therapy for newly diagnosed Ph^+ ALL has yet to be investigated. The question is posed: can single-agent TKIs be used as induction therapy for newly diagnosed Ph^+ ALL, thereby not only decreasing the complications and toxicities lead to treatment related death (TRM), but also decreasing the "financial toxicity" created by combination therapy? Here, we report for the first time a newly diagnosed Ph^+ ALL patient with pulmonary infection treated with single-agent dasatinib.

2. Case description

A 59-year-old man was admitted to our hospital due to fever and abnormal hemogram (white blood cell count 20×10^9/L and

Editor: N/A.

The authors declare no conflict of interest.

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Medicine (2018) 97:38(e12308)

Received: 24 April 2018 / Accepted: 16 August 2018

http://dx.doi.org/10.1097/MD.0000000000012308

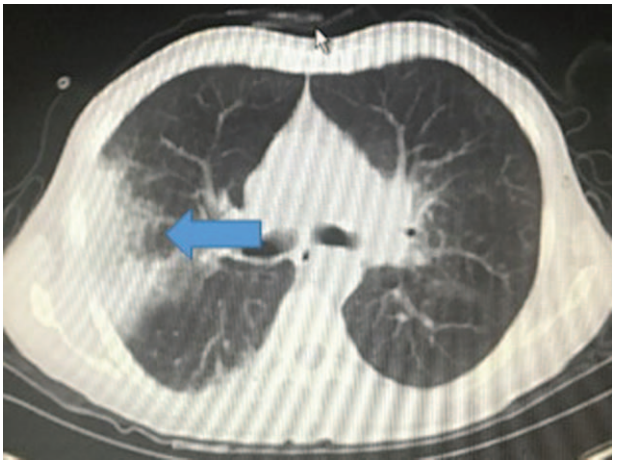

Figure 1. The chest CT of the patients. The chest CT showed serious infection (arrow).

platelet count 18.4×10^9/L). The patient was diagnosed with Ph^+ ALL with 93% blast cells and 84.5% BCR/ABL gene expression, as measured by real-time quantitative polymerase chain reaction (RT-qPCR) and a *t* (9, 22) karyotype. Chest CT revealed severe infection (Fig. 1). Sputum and blood cultures were both negative for bacterial and/or fungal growth. The patient was treated with tienam, teicoplanin, and itraconazole for his lung infection. Oral dasatinib (100 mg qd) was also used for Ph^+ ALL induction therapy for 28 days. After 5 days of dasatinib treatment, the patient exhibited dyspnea and wet pulmonary rale in the lung. Dasatinib treatment was discontinued, and itraconazole was replaced with voriconazole treatment of fungal lung infection. Approximately 3 weeks later, the patient's infection was controlled and his hemagram appeared normal. Bone marrow (BM) examination showed 1% blast cells. In total, 25.7% of BM were blast cells, as detected by flow cytometry (FCM). Fluorescence in situ hybridization (FISH) revealed 6% Ph^+ cells, and BCR/ABL gene expression was only 6% as observed by RT-qPCR. The patient continued to receive oral dasatinib (100 mg qd) treatment after recovery of dyspnea. Four weeks after the patient resumed use of dasatanib, FISH analysis determined that 0% of BM cells were Ph^+ cells and minimal residual disease (MRD) detection by FCM was negative. The BCR/ABL gene expression was also determined to be 0% as detected by RT-qPCR. This patient subsequently refused chemotherapy treatment and left our hospital. This study was approved by the ethics committee of Xinqiao Hospital and written informed was obtained from the patient in accordance with the Declaration of Helsinki. The patient has provided informed consent for the use of his case in publication and gave permission to be included in the manuscript.

3. Discussion

The severity of both infectious and non-infectious toxicities in induction chemotherapy that lead to early, excessive TRM are a primary concern for Ph^+ ALL patients treated with long-term chemotherapy or chemotherapy in combination with TKIs.[6]

Previously, the combination of cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) was the primary chemotherapy regimen for induction therapy in newly-diagnosed Ph^+ ALL patients. However, Ph^+ ALL patients considered to have a good prognosis were shown to benefit from early administration of TKIs. Thus, TKIs were added to multi-agent chemotherapy regimens to improve induction remission in these patients. In one study, TKIs combined with hyper-CVAD were used to treat 34 Ph^+ ALL patients with 96% CR; however, numerous grade 3 and 4 toxicities occurred, including 12 episodes of bleeding. In addition, a total of 5 episodes of pleural effusion and 2 episodes of pericardial effusion—all noted grade 3/4 severity. Other serious grade 3/4 adverse events included episodes of neutropenic infections, acute renal failure, reduced liver function, diarrhea, hyperbilirubinemia, hypocalcemia, hypophosphatemia, and hypokalemia.[7] In a separate study, TKIs were combined with low-intensity chemotherapy (weekly 2 mg of vincristine and 40 mg of dexamethasone for 2 days for 4 weeks) and also resulted in 96% complete remission for 71 Ph^+ ALL patients over 55 years of age. However, during induction, 13 patients exhibited bacteremia or septicemia (4 cases of Gram-negative; 9 of Gram-positive strains), and 2 patients developed nonbacterial lung infections.[2] Finally, TKIs combined with glucocorticoids were also used to reduce chemotherapy related toxicities. Although no deaths or relapses occurred during induction, 4 patients discontinued treatment due to toxicity (fever, pleural effusion, nausea vomiting, proteinuria, and hypertransaminasemia).[3] Thus, complications remain the primary concern in current combinatorial approaches for induction therapy in newly diagnosed Ph^+ ALL.

Can single-agent TKIs be used to treat Ph^+ ALL patients as induction monotherapy to decrease the complications that lead to increased TRM in patients treated with combination therapy? As a hint, a recent report tested the efficacy, safety, and tolerability of single-agent dasatinib (gradually increased from 70 mg^2/d to 200 mg^2/d) was assessed in 36 imatinib-resistant or imatinib-intolerant adult Ph^+ ALL patients who underwent prior HSCT or received prior chemotherapy or IFN-α, and previously received imatinib.[5] With a minimum follow-up of 8 months, the results revealed that 42% (15/36) of patients achieved major hematologic responses, 58% (21/36) of patients attained complete cytogenetic responses, and 6% (2/36) of patients discontinued therapy as a result of study-drug toxicity with grade 1 or 2 adverse events. Febrile neutropenia was the most frequent severe-adverse event, but this condition and other cytopenias were manageable with dose reduction. Thus, dasatinib appears to represent a safe and effective treatment option and reflects an important therapeutic advance for refractory/relapsed Ph^+ ALL patients. However, this study performed a relatively short-term follow-up. It is unclear whether the single-agent dasatinib monotherapy can be used in induction therapy for newly diagnosed Ph^+ ALL.

In this study, we are the first to report, to our knowledge, that single-agent dasatinib induced complete remission in a newly-diagnosed elderly Ph^+ ALL patient with good outcome, even though this patient simultaneously suffered from pulmonary infection. Although some data suggest that the single-agent TKIs can be used as induction therapy in the first-line treatment for newly diagnosed Ph^+ ALL patients, these protocols do not truly reflect "monotherapy" due to these studies' use of chemotherapy in the pre-treatment or in combination with induction therapy, which differs from our report of single-agent dasatinib alone (Table 1).[3,8]

Table 1

Compare the protocol for tyrosine kinase inhibitors as the first-line in induction therapy for newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia.

Author	Prephase	Induction therapy	Complete remission (%)	Follow-up	Reference
Zhang C, et al	No	Dasatinib (100 mg qd) for 28 days	100	At day 28	Our report
Ottmann OG, et al	Dexamethasone: 10 mg/m^2 d1–5; cyclophosphamide: 200 mg/m^2 d3–5; methotrexate: 12 mg dL	Imatinib (600 mg/d) for 28 days	96.3	At 4 wks	8
Robin Foà, et al	Prednisone (10–60 mg/m^2/d) for 7 days	Dasatinib (70 mg twice daily) for 32 days Prednisone 60 mg/m^2 per day (capped at 120 mg daily) was administered until day 24 and then tapered and stopped at day 32	92.5	At day 22	3

4. Conclusion

This is the first report on the use of single-agent dasatinib monotherapy in the absence of other drugs (including corticosteroids) for induction therapy in the treatment of a newly diagnosed Ph$^+$ ALL patient to induce complete remission and negative MRD (detected by RT-qPCR and FCM). As a second-generation TKI, exhibits increased efficacy compared with first-generation TKIs, such as imatinib, as it inhibits the multi-targeted both the active and inactive conformations of the ABL kinase and SRC family kinases, except for T315I. The use of single-agent dasatinib for induction therapy decreases the complications and toxicities compared with multi-agent chemotherapy regimens, which not only saves the patient money, but also decreases the risk of death during induction therapy and subsequently increases the number of patients available to receive allo-HSCT. Recent reports suggest that the MRD status (BCR/ABL <0.01%; mostly detected by RT-qPCR) may not influence the long-term outcomes of adults Ph$^+$ ALL patients having undergone allogeneic HSCT (allo-HSCT).[9–11] Therefore, the single-agent dasatinib monotherapy for induction therapy followed by allo-HSCT may represent a promising new model in the treatment of newly-diagnosed adult Ph$^+$ ALL patients.

Author contributions

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Supervision: Cheng Zhang, Xi Zhang.
Validation: Cheng Zhang, Xi Zhang.
Visualization: Cheng Zhang, Xi Zhang.
Writing – original draft: Cheng Zhang.
Writing – review & editing: Cheng Zhang, Xi Zhang.

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