Crizotinib as Salvage and Maintenance With Allogeneic Stem Cell Transplantation for Refractory Anaplastic Large Cell Lymphoma

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Abstract

The NPM-ALK fusion protein is found in ALK⁺ anaplastic large cell lymphomas harboring the t(2;5) chromosomal translocation. Patients harboring ALK translocations typically have an excellent prognosis with conventional chemotherapy and a reported 5-year survival rate of 70%. Although most patients with ALK⁺ anaplastic large cell lymphoma have a good prognosis, some patients do not respond to standard therapies. In patients with refractory anaplastic large cell lymphoma who can achieve remission, allogeneic stem cell transplant is a potentially curative option. This article describes a patient with refractory ALK⁺ anaplastic large cell lymphoma who experienced a complete response to the ALK inhibitor crizotinib and then underwent an allogeneic stem cell transplant followed by crizotinib maintenance therapy. (*J Natl Compr Canc Netw* 2014;12:323–326)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Discuss the clinical activity of crizotinib in the management of patients with anaplastic large cell lymphoma

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The NPM-ALK fusion protein is found in ALK⁺ anaplastic large cell lymphomas harboring the t(2;5) chromosomal translocation.¹ Patients harboring ALK translocations typically have an excellent prognosis with conventional chemotherapy and a reported 5-year survival rate of 70%.² Although most patients with ALK⁺ anaplastic large cell lymphoma have a good prognosis, some do not respond to standard therapies. In patients with refractory anaplastic large cell lymphoma who can achieve remission, allogeneic stem cell transplant is a potentially curative option.³ In a retrospective analyses of 27 patients with anaplastic large cell lymphoma who underwent an allogeneic stem cell transplant, Le Gouill et al⁴ found a 55% 5-year survival rate. This article describes a patient with refractory ALK⁺ anaplastic large cell lymphoma who experienced a response to the ALK inhibitor crizotinib and underwent an allogeneic stem cell transplant.⁵

Case Summary

A 34-year-old man presented with lymphadenopathy and right arm edema. Pathology revealed anaplastic large cell lymphoma. Immunohistochemistry was positive for ALK1 and fluorescence in situ hybridization analysis demonstrated a t(2;5) chromosomal translocation. The patient's anaplastic large cell lymphoma was refractory to standard treatment, and he progressed through 8 lines of chemotherapy in 11 months. The patient was unsuccessfully treated with CHOP, gemcitabine-based therapy, pralatrexate, high-dose methotrexate when he developed central nervous system (CNS) involvement, and brentuximab.

After these treatments, the patient was consented and enrolled in an experimental protocol testing crizotinib in patients with advanced cancers refractory to standard therapy (ClinicalTrials.gov identifier: NCT00585195). The trial was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board and was in accordance with the Declaration of Helsinki. At the time of enrollment, the patient had a large confluent mass that involved the entire lateral and posterolateral chest wall, and measured 13.4 cm in largest axial diameter and 30.5 cm in craniocaudal measurement. The patient reported that the mass was rapidly enlarging and extremely painful. His LDH level was elevated at 347 U/L. On

the experimental protocol, the patient was treated with crizotinib, 250 mg twice a day. Crizotinib was well tolerated and no signs were seen of tumor lysis. Symptomatic improvement was seen within 3 days, and a restaging PET/CT scan performed 8 weeks later showed a complete metabolic response. Figure 1 shows a comparison of the baseline PET/CT scan (Figure 1A) with the PET/CT scan obtained after 8 weeks of crizotinib treatment (Figure 1B).

Thirteen weeks after starting crizotinib, the patient underwent a myeloablative hematopoietic stem cell transplant and received peripheral blood stem cells from a fully matched unrelated donor. Crizotinib was stopped a day before he started the conditioning regimen of cyclophosphamide and total body irradiation. The transplant was well tolerated, except for an episode of asymptomatic cryptogenic organizing pneumonia that responded to steroids. At 21 days after stem cell infusion, the patient was able to restart the experimental protocol of crizotinib. Upon restarting, the patient initially experienced transient thrombocytopenia. Titration of tacrolimus was challenging because of the drug interaction between tacrolimus and crizotinib (crizotinib is a CYP3A4 inhibitor). At the time of writing, it has been 33 months since the patient first started crizotinib. He has been on maintenance crizotinib for 30 months and is experiencing complete remission according to PET/CT.

Figure 1 PET/CT scan at (A) baseline and (B) 8 weeks after crizotinib treatment.

Discussion

Preclinical data have shown that ALK tyrosine kinase activity is essential to the survival of ALK⁺ anaplastic large cell lymphoma cell lines.⁶ Consistent with this, case reports have shown the activity of crizotinib in ALK⁺ anaplastic large cell lymphoma.^{7,8} In a pediatric phase I trial, 7 of 8 patients with anaplastic large cell lymphoma experienced a complete response after treatment with crizotinib.⁹ Similar to the present case, Ordemann et al⁸ reported a case in which crizotinib treatment followed by brentuximab served as a bridge to allogeneic stem cell transplant.

In the present patient, crizotinib did not interfere with the ability to perform an allogeneic stem cell transplant, and was safely reintroduced as maintenance therapy after transplant. This suggests the feasibility of using crizotinib as a bridge to allogeneic stem cell transplant and as maintenance therapy after transplant. Given the drug-drug interaction between crizotinib and tacrolimus, the dosage of tacrolimus must be carefully monitored in the post-transplant setting.

Seven months before starting crizotinib, the patient had evidence of lymphoma in his cerebrospinal fluid (CSF). He was treated with high-dose methotrexate and has had no evidence of CNS recurrence since that time. Interestingly, crizotinib does not seem to have a high penetrance into the CNS. Pharmacokinetic analysis of a patient with lung cancer treated with crizotinib showed that the concentration of crizotinib was much lower in the CSF than in the plasma.¹⁰ Consistent with this, the CNS is a frequent area of recurrence in patients with lung cancer treated with crizotinib.^{11,12}

It is impossible to know the relative contributions of crizotinib and the allogeneic stem cell transplantation in this patient. In EML4-ALK-rearranged non-small cell lung cancer, patients inevitably develop resistance to crizotinib, and the median progression-free survival in this population is 9.7 months.¹³ However, data on the long-term effectiveness of crizotinib in anaplastic large cell lymphoma are much more limited. A recent report by the Children's Oncology Group described 2 pediatric patients whose anaplastic large cell lymphoma continued to respond to crizotinib after treatment with the drug for at least 2 years.⁹ Data on the long-term effectiveness of allogeneic stem cell transplantation in patients with refractory anaplastic large cell lymphoma are also limited.

One case series showed that the 5-year survival rate for patients with anaplastic large cell lymphoma was 55% after allogeneic stem cell transplantation.⁴

Therefore, the long remission obtained for the present patient could reflect ongoing disease control by crizotinib or a successful graft-versus-lymphoma effect. It is also possible that both therapies are contributing to the patient's long-term disease control.

Despite these encouraging responses in ALK⁺ anaplastic large cell lymphoma, whether other ALK⁺ lymphomas will have the same sensitivity is unclear. We have also treated a 29-year-old woman whose refractory ALK⁺ large B-cell lymphoma rapidly progressed through treatment with crizotinib.¹⁴ Further investigation is needed to explore whether the crizotinib resistance seen in this patient is generalizable. It is possible that the ALK kinase domain plays different roles in the oncogenesis of ALK⁺ large B-cell lymphoma and ALK⁺ anaplastic large cell lymphoma.

Conclusions

New treatments for patients with refractory ALK⁺ anaplastic large cell lymphoma are greatly needed. An emerging series of case reports suggests that crizotinib may be an effective treatment in this disease.⁷⁻⁹ The present case report highlights the possibility of using crizotinib both as a bridge to allogeneic stem cell transplant and as maintenance therapy after transplant.

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Posttest Questions

1. Most patients with ALK⁺ anaplastic large cell lymphoma are curable with conventional chemotherapy.
 - a. True
 - b. False
2. Allogeneic stem cell transplant is a potentially curative option for patients with refractory anaplastic large cell lymphoma who can achieve a remission.
3. Which of the following is considered an adverse effect of crizotinib?
 - a. Asymptomatic cryptogenic organizing pneumonia
 - b. Transient thrombocytopenia
 - c. A and B
 - d. None of the above