Received: 2 November 2018 | Revised: 7 January 2019 | Accepted: 18 January 2019

DOI: 10.1002/pbc.27645

BRIEF REPORT

WILEY Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology

ALK inhibition in two emblematic cases of pediatric inflammatory myofibroblastic tumor: Efficacy and side effects

Erica Brivio[1] | **C. Michel Zwaan**[1,2]

[1]Prinses Maxima Centrum, Center for Pediatric Oncology, Utrecht, the Netherlands

[2]Department of Pediatric Oncology/Hematology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands

Correspondence
C. Michel Zwaan, Department of Pediatric Oncology/Hematology, Erasmus MC-Sophia Children's Hospital, Wytemaweg 80, 3015 CN Rotterdam, the Netherlands.
Email: c.m.zwaan@erasmusmc.nl

Abstract

There is an increasing interest for anaplastic lymphoma kinase (ALK) inhibitors in pediatric oncology for specific entities such as ALK-driven inflammatory myofibroblastic tumor (IMT). IMT treatment can be challenging due to localization of the tumor and in rare cases of metastasis. When standard surgical treatment is not feasible, ALK inhibitors may play an important role, as recently reported for the first-generation ALK inhibitors (crizotinib). However, data on the second-generation ALK inhibitors are limited. We report two emblematic cases of IMT in pediatric patients, treated with the second-generation ALK inhibitor ceritinib in the context of a clinical trial (NCT01742286).

KEYWORDS

ALK inhibitors, ceritinib, inflammatory myofibroblastic tumor, pediatric oncology

1 | INTRODUCTION

There is an increasing interest in anaplastic lymphoma kinase (ALK) inhibitors for treatment of pediatric malignancies that are *ALK* or *ROS* fusion gene driven, among others inflammatory myofibroblastic tumor (IMT) and anaplastic large-cell lymphoma, as recently highlighted in the report from the Paediatric Strategy Forum for ALK Inhibition.[1]

IMT is a mesenchymal neoplasm characterized by a spindle cell proliferation with an inflammatory infiltrate, occurring primarily during the first two decades of life. Rearrangements involving the *ALK* locus have been documented in approximately 50% of IMTs and may define a subgroup of IMTs sensitive to targeted kinase inhibition.[2]

Although IMT are considered by the World Health Organization to be of "intermediate malignancy", treatment can be challenging because of the localization of the tumor, leading to difficult or impossible surgical resection with potentially severe mutilation. Moreover, in rare cases, metastasis can occur.[3] When standard surgical treatment is not feasible, ALK inhibitors may play an important role in reducing tumor volume. A Children's Oncology Group (COG) report and a recently published review show the promising efficacy of the first-generation ALK inhibitors (crizotinib) in IMT.[2,4] In addition, case reports on a few patients treated with ceritinb have been published.[5–8]

We here report on two emblematic cases of IMT in pediatric patients, treated with the second-generation ALK inhibitor ceritinib in the context of a clinical trial (NCT01742286).

2 | CASE REPORTS

2.1 | Patient 1

The first case is a stage 4 IMT, initially presenting in a 9-year-old male child patient, with a primary lesion in the elbow region. Over a time period of 8 years, the patient was offered various lines of treatment, including nonradical resection, as well as non-steroidal anti-inflammatory drugs and metronomic chemotherapy with methotrexate and vinorelbine. When the patient was 17 years old, a stage 4 relapse with lung metastasis was detected. FISH on archived tumor material revealed the presence of an *ALK* translocation, and the patient started treatment with the second-generation ALK inhibitor ceritinib at a dose of 300 mg/m^2/day (500 mg/day). A response was evident after 6 weeks of treatment, and a complete remission (CR) was reached in 6 months, with almost full regression of lung metastasis on computed tomography (CT) scans. After 2 years of treatment with

Abbreviations: ALK, anaplastic lymphoma kinase; CML, chronic myeloid leukemia; COG, Children's Oncology Group; CR, complete remission; IMT, inflammatory myofibroblastic tumor; PR, partial remission; TKI, tyrosine kinase inhibitor; ULN, upper limit of normal

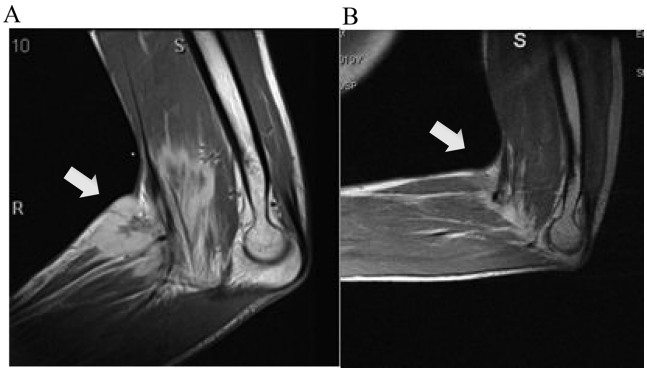

FIGURE 1 Patient 1—A, Magnetic resonance imaging at second local relapse of the inflammatory myofibroblastic tumor in the elbow; B, regression after 2 months of treatment with ceritinib

persistent CR, an elective discontinuation of treatment was attempted, but unfortunately after 2 months a local relapse was evident, also with renewed progression of the lung metastasis. Ceritinib was restarted at a dose of 600 mg/day, outside the clinical trial. This led again to CR after 2 months of treatment (Figure 1). The only side effects that occurred were mild gastrointestinal complaints and an increase in serum creatinine (maximum grade 1—starting from 0.7 mg/dL, going up to a maximum of 1.3 mg/dL), with a rapid recovery during treatment discontinuation (decreased to 0.9 mg/dL). The effect on creatinine values has already been reported for other ALK inhibitors like crizotinib and might be related to interference with the tubular secretion of creatinine.[9] Considering the side effects and the fast complete response, the dose was reduced to 450 mg/day, which was safely continued till now. Currently, the patient is 22 years old and in CR for 3 years since the therapy was restarted.

2.2 | Patient 2

The second case is a 14-year-old male patient presenting with persistent hematuria and diagnosed with an IMT localized in the bladder wall. FISH was positive for an *ALK* translocation in approximately 50% of the tumor cells, and immunohistochemistry showed ALK expression. To avoid a destructive surgical resection, neo-adjuvant treatment with ceritinib was attempted at the dosage of 450 mg/m^2/day (800 mg/day). After 2 months of treatment, the patient experienced a severe toxicity with acute liver and renal failure, which led to a prompt and definitive discontinuation of treatment with ceritinib. The maximum level of transaminases that was reached was 15,000 U/L for glutamic oxaloacetic transaminase and 8,600 U/L for glutamic pyruvic transaminase (≫ 10×ULN, where ULN is upper limit of normal), with a total bilirubin level of 4 mg/dL (> 3 × ULN). No infections were demonstrated, and other possible causes were excluded by imaging and blood tests. We concluded this might be a case of drug-induced liver injury (Hy's Law), as already reported for others ALK inibitors.[10,11] Moreover, tyrosine kinase inhibitors (TKIs) can inhibit paracetamol glucuronidation, and the interaction of the two drugs may have played a role in our patient, who was taking paracetamol for preexisting "abdominal pain".[12] Despite extensive infectious work-up which was negative, a viral infection may also have played a role, as the patient was suffering from a common cold. One month after the start of symptoms, a complete recovery from hepatic injury was obtained. At this point, after 2 months of treatment and 1 month of wash-out due to the toxicity, a magnetic resonance imaging evaluation revealed a 70% reduction of the tumor size, and the patient underwent complete surgical resection preserving the integrity of the bladder (Figure 2). Currently, the patient is in continuous CR now 3 years from surgical resection, without any additional treatment and with normal liver function.

3 | DISCUSSION

These two cases show the different important role of ALK inhibitors for IMT treatment strategy as neo-adjuvant treatment and for metastatic disease.

Promising activity was recently reported in a COG study on ALK inhibition with crizotinib, including 14 IMT patients. This Phase I/II trial showed CR or partial remission (PR) in 36% and 50% of patients with either metastatic or inoperable ALK-positive IMT. At the time of the study report, 10 out of 12 patients in CR or PR discontinued treatment, but the follow up is not reported, thus it is unknown if these patients subsequently relapsed or not.[2] In addition, a retrospective collection of 30 IMT cases from the literature (including the above-mentioned study) showed CR in 40% and PR in another 40% of patients, after treatment with crizotinib. All the patients reported had an unresectable or multifocal disease, representing a subgroup in

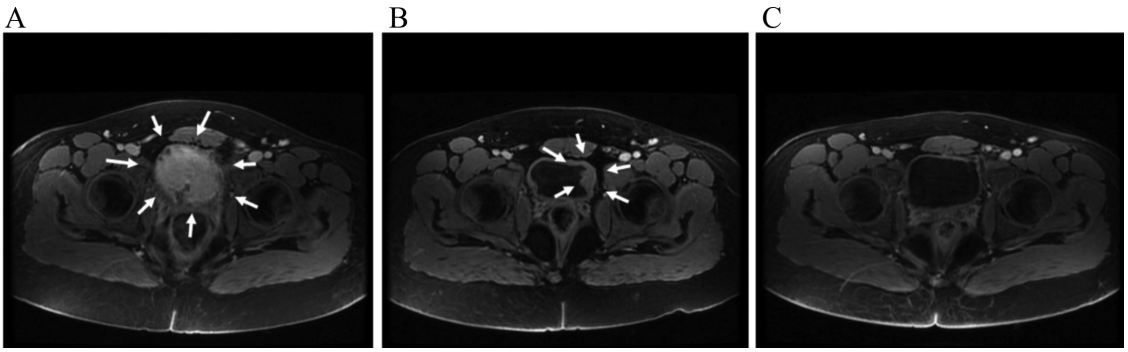

FIGURE 2 Patient 2—A, Inflammatory myofibroblastic tumor of the bladder at diagnosis; 2, reduction of tumor size after 3 months of therapy with ceritinib; C, complete resection after surgery

which ALK inhibitors may play a crucial role. Again, the follow-up after crizotinib discontinuation, if occurred, was not reported.[4]

One of the major limitations of ALK inhibitors is acquired tumor cells resistance developed during treatment.[13] This occurred also in two patients treated for IMT with crizotinib and reported by Thailen et al., showing a progression of disease after 2 and 8 months of continuous treatment.[4] Nevertheless, our first case suggests the existence of a pattern already known for other diseases, such as in chronic myeloid leukemia (CML), where patients who electively discontinue TKIs after achieving long-lasting complete molecular remission and subsequently fail during the treatment-free period might remain sensitive to retreatment with the same inhibitor.[14] This case reveals the intriguing possibility that the experience in CML could be potentially translated to ALK inhibition in IMT, which is probably also mainly driven by the ALK fusion as a "monogenic" event.

The second patient shows the potential of ALK inhibitors in newly diagnosed and/or relapsed unresectable disease. Recently, another case report highlighted the efficacy of ALK inhibitors (crizotinib) as neo-adjuvant treatment in an IMT of the urinary bladder, resulting in avoidance of radical cystectomy in a 17-year-old patient.[15] Further investigations need to be performed in newly diagnosed and/or relapsed unresectable IMTs with ALK inhibitors to see whether this results in higher cure rates by increasing the rate of radical surgical resections with less mutilation. A study with crizotinib in this respect is underway (EudraCT number 2015-005437-53).

CONFLICTS OF INTEREST

Novartis provided the drug and reimbursement of study-related costs but had no influence on the content of the paper.

ACKNOWLEDGMENTS

The authors would like to thank Novartis for agreeing to publish these cases, treated in the context of the clinical trial LDK378X2103.

ETHICAL STATEMENT

Informed consent, required by applicable law, from patients and/or parents, whose information is included in the article, has been properly obtained.

ORCID

Erica Brivio https://orcid.org/0000-0001-5285-1702

REFERENCES

1. European Medicines Agency. Paediatric strategy forum for anaplastic lymphoma kinase (ALK) inhibition in paediatric malignancies. EMA/210027/2017 Report. 2017.
2. Mossé YP, Voss SD, Lim MS, et al. Targeting ALK with crizotinib in pediatric anaplastic large cell lymphoma and inflammatory myofibroblastic tumor: a Children's Oncology Group Study. *J Clin Oncol*. 2017;35:3215-3221.
3. Gleason BC, Hornick JL. Inflammatory myofibroblastic tumours: where are we now. *J Clin Pathol*. 2008;61:428-437.
4. Theilen TM, Soerensen J, Bochennek K, et al. Crizotinib in ALK+ inflammatory myofibroblastic tumors—current experience and future perspectives. *Pediatr Blood Cancer*. 2018;65:e26920.
5. Mansfield AS, Murphy SJ, Harris FR, et al. Chromoplectic TPM3–ALK rearrangement in a patient with inflammatory myofibroblastic tumor who responded to ceritinib after progression on crizotinib. *Ann Oncol*. 2016;27:2111-2117.
6. Yuan C, Ma MJ, Parker JV, Mekhail TM. Metastatic anaplastic lymphoma kinase-1 (ALK-1)-rearranged inflammatory myofibroblastic sarcoma to the brain with leptomeningeal involvement: favorable response to serial ALK inhibitors: a case report. *Am J Case Rep*. 2017;18:799-804.
7. Ono A, Murakami H, Serizawa M, et al. Drastic initial response and subsequent response to two ALK inhibitors in a patient with a highly aggressive ALK-rearranged inflammatory myofibroblastic tumor arising in the pleural cavity. *Lung Cancer*. 2016;99:151-154.
8. Parker B, Parker JV, Lymperopoulos A, Konda V. A case report: pharmacology and resistance patterns of three generations of ALK inhibitors in metastatic inflammatory myofibroblastic sarcoma. *J Oncol Pharm Pract*. 2018;1:1-5.
9. Izzedine H, El-Fekih RK, Perazella MA. The renal effects of ALK inhibitors. *Invest New Drugs*. 2016;34:643-664.
10. Sassier M, Mannecier B, Gschwend A, et al. Successful treatment with ceritinib after crizotinib induced hepatitis. *Lung Cancer*. 2016;95:15-16.
11. Robles-Diaz M, Lucena MI, Kaplowitz N, et al. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. *Gastroenterology*. 2014;147:109-118.
12. Yong L, Jacqueline R, Mark JR. Inhibition of paracetamol glucuronidation by tyrosine kinase inhibitors. *Br J Clin Pharmacol*. 2011;71:917-920.
13. Hideko I, Nagio T, Katsuyuki K. Mechanisms of acquired resistance to ALK inhibitors and the rationale for treating ALK-positive lung cancer. *Cancers*. 2015;7:763-783.
14. Saußele S, Richter J, Hochhaus A, Mahon F. The concept of treatment-free remission in chronic myeloid leukemia. *Leukemia*. 2016;30:1638-1647.
15. Nagumo Y, Maejima A, Toyoshima Y, et al. Neoadjuvant crizotinib in ALK-rearranged inflammatory myofibroblastic tumor of the urinary bladder: a case report. *Int J Surg Case Rep*. 2018;48:1-4.

How to cite this article: Brivio E, Zwaan CM. ALK inhibition in two emblematic cases of pediatric inflammatory myofibroblastic tumor: Efficacy and side effects. *Pediatr Blood Cancer*. 2019;66:e27645. https://doi.org/10.1002/pbc.27645