

## Complete response with crizotinib in two children with chemotherapy resistant neuroblastoma

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Dear Editor,

A 2-year-old girl was diagnosed with stage IV neuroblastoma with initial disease sites being right adrenal mass and bone marrow (BM) with nonamplified *MYCN*. She received treatment as per high risk-neuroblastoma-1 (HR-NBL-1)/ESIOP protocol<sup>[1]</sup> and remained disease free for 22 months when she relapsed in the BM and lung. She received cyclophosphamide-topotecan alternate with ifosfamide-carboplatin-etoposide based salvage chemotherapy with no response after six cycles. Immunohistochemical (IHC) for anaplastic lymphoma kinase (ALK) protein using D5F3 antibody in the biopsy specimen showed strong and uniform expression of ALK. Crizotinib capsule 200 mg twice a day (265 mg/m<sup>2</sup>/dose) was started after informed consent as palliation, with monitoring of blood counts, liver, and kidney function. She tolerated the drug well apart from mild nausea. She improved symptomatically and evaluation after 16 weeks revealed complete response in BM and lung. Parents declined the option of hematopoietic stem cell transplant; hence, crizotinib monotherapy was continued. She remained disease-free for a total 32 weeks when she presented with fever and body ache and was confirmed to have a relapse in BM. The second case is a 2-year-old girl who was diagnosed as a case of high-risk neuroblastoma involving right suprarenal, BM and multiple bony sites. She was treated as per HR-NBL-1/ESIOP protocol. BM disease persisted at the end of chemotherapy. Cyclophosphamide-topotecan based chemotherapy was administered as salvage with no change in disease status after two cycles. Hence, ALK protein was tested by IHC and strong expression of ALK led to the addition of crizotinib 125 mg twice

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a day (250 mg/m<sup>2</sup>/dose) to the salvage chemotherapy. Marrow evaluation after two such cycles showed clearance of metastatic disease after which she received autologous stem cell transplant, radiation, and differentiation therapy as per protocol. No side effects were observed with the use of crizotinib during this period. She remains disease-free and off therapy for 2 months.

Chemo-resistant and relapsed neuroblastoma have a poor outcome with conventional multimodality therapy. Genomic studies have revealed two genes which can be therapeutically targeted, ALK and *MYCN*. Trials targeting ALK in neuroblastoma have progressed rapidly because of oral bioavailability of crizotinib and established safety profile in adult patients with ALK-positive nonsmall cell lung cancer (NSCLC).

Activating mutation in the tyrosine kinase domain of ALK was discovered as the most common cause of familial neuroblastoma and about 10–15% of sporadic neuroblastoma cases.<sup>[2]</sup> Crizotinib an ATP-competitive pyrimidinedamine derivative is a small molecule competitive inhibitor of ALK and mesenchymal-epithelial transition kinase that has shown extraordinary results with very little toxicity in various adult tumors harboring ALK translocations. Experience with crizotinib in children with refractory neuroblastoma in the COG trial ADVL0912 showed encouraging results with crizotinib monotherapy.<sup>[3]</sup>

DNA sequencing for ALK mutations is the gold standard for diagnosing these mutations, however as the pretreatment frozen tissue is often not available as in our case IHC testing with D5F3 antibody for ALK expression or by FISH for ALK mutation is considered a valid alternative; although, it signifies only ALK amplification.<sup>[4]</sup>

In our first patient, crizotinib monotherapy was able to achieve a complete response in a chemotherapy resistant setting and furthermore sustained this response for 32 weeks. In the second patient, crizotinib helped achieve remission in a primary refractory patient thereby making her eligible for autologous stem cell transplant.

Crizotinib therapy is well-tolerated and most common adverse events observed are minor which include nausea, diarrhea, vomiting, and vision disorders. Severe side effects are rare and include asymptomatic elevations in aminotransferase levels and fatigue. Neither of our patients showed any clinical or metabolic adverse effect at a dose of 250–265 mg/m<sup>2</sup>/dose over 2–9 months.

As with other tyrosine kinase inhibitors, use of crizotinib as monotherapy leads to the emergence of resistance, as is also observed in adult patients with NSCLC. Genetic analysis suggests that mutations within ALK kinase domain or up-regulation of an alternative signaling pathway are the likely mechanisms of resistance.

We observed complete response with crizotinib in two pediatric patients with chemotherapy-resistant ALK-positive neuroblastoma. Oral bioavailability and safety profile of this agent makes it ideal for use in heavily pretreated patients, although monotherapy is known to lead to resistance. Encouraging results in refractory tumors makes a strong case for its use in combination with other agents as frontline therapy for high-risk neuroblastoma conventionally associated with poor prognosis.

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#### Conflicts of interest

There are no conflicts of interest.

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#### References

- Balwierz W, Wiczorek A, Klekawka T, Garus K, Bolek-Marzec K, Perek D, *et al*. Treatment results of children with neuroblastoma: Report of Polish Pediatric Solid Tumor Group. *Przegl Lek* 2010;67:387-92.
- Carpenter EL, Mossé YP. Targeting ALK in neuroblastoma – Preclinical and clinical advancements. *Nat Rev Clin Oncol* 2012;9:391-9.
- Mossé YP, Lim MS, Voss SD, Wilner K, Ruffner K, Laliberte J, *et al*. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: A Children's Oncology Group phase 1 consortium study. *Lancet Oncol* 2013;14:472-80.
- Yan B, Kuick CH, Lim M, Venkataraman K, Tennakoon C, Loh E, *et al*. Platform comparison for evaluation of ALK protein immunohistochemical expression, genomic copy number and hotspot mutation status in neuroblastomas. *PLoS One* 2014;9:e106575.

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