Sorafenib treatment in children with relapsed and refractory neuroblastoma: an experience of four cases

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Keywords
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Abstract
Metastatic neuroblastoma is an aggressive malignancy with a poor prognosis. Recent findings have shown that sorafenib decreases cell viability and increases apoptosis in human neuroblastoma cell lines. We report an experience of compassionate use of sorafenib in children with treatment-refractory neuroblastoma. Sorafenib showed transient anti-tumor activity in all four patients without adverse effects. However, progression was observed after a short stabilization phase. While sorafenib showed minimal anti-tumor activity in our patients, it might still be effective in patients with neuroblastoma in an earlier stage.

Patients and Methods
Patients <25 years of age with recurrent treatment-refractory neuroblastoma with either presence of a measurable tumor or a neuron-specific enolase (NSE) level >20 ng/mL (the upper limit of normal in our institution) were eligible. Other eligibility criteria included Karnofsky/
Lansky performance score ≥30%, no hepatic failure, no uncontrolled systemic hypertension, no prior thromboembolic event, and no metastasis within the brain parenchyma. Patients were excluded if they had had active other cancer within 5 years, or if they were pregnant or lactating. This trial was approved by Osaka City General Hospital institutional review board. Informed consent was obtained from parents of the children.

Sorafenib was administered orally, twice daily, continuously for at least 14 days. Capsules (200 mg) were dissolved in warm water for administration to children who could not swallow capsules. The starting dose was 150 mg/m². The dose was rounded off to the nearest multiple of 200 mg. Because sorafenib has a half-life of >24 h [11], administration of a doubled dose once daily was allowed when a 200-mg capsule was too much when body surface area was small. If the anti-tumor effect was insufficient after administration for 14 days without adverse events, dose escalation to 250 mg/m² was allowed according to the physician’s decision. Treatment was continued in the absence of marked disease progression. Treatment was stopped if any Grade 4 hematologic or Grade 3–4 nonhematologic toxicity remained after 30-day discontinuation of sorafenib or if the patient no longer wanted to receive the study drug. Toxicity was graded according to CTCAE v4.0.

Results

From June 2012 to February 2013, four patients (aged 4–5 years) with relapsed neuroblastoma were treated with sorafenib. Table 1 summarizes their disease characteristics, treatment, and outcome.

Table 1. Patient characteristics.

| Pt no. | Age, year | Sex | MYCN | Time to 1st relapse, months | Time from 1st relapse (onset) to sorafenib initiation, months | Salvage therapy | Disease sites at sorafenib initiation | Duration of sorafenib administration, days | Clinical outcome |
|--------|-----------|-----|------|----------------------------|-------------------------------------------------------------|----------------|-------------------------------------|--------------------------------------------|-----------------|
| 1      | 5         | M   | +    | 21                         | 12 (33)                                                     | CPT-11, Zol, RTx | Bone (multiple), Liver, Spleen, LN | 37                          | DOD at 34 months from onset |
| 2      | 5         | M   | +    | 21                         | 13 (34)                                                     | CPT-11/IFO, TMZ/ETP, VNR/CPA, RTx | Bone (multiple), Liver, Kidney, Lung, LN | 56                          | DOD at 36 months from onset |
| 3      | 4         | F   |  −   | 12                         | 8 (20)                                                      | CPT-11, Zol, TBI | Bone (multiple), Lung, LN         | 21                          | DOD at 34 months from onset |
| 4      | 4         | F   | +    | 17                         | 16 (33)                                                     | CPT-11, Zol, RTx | Bone (multiple), Pleura, Subcutaneous nodule, LN | 33                          | DOD at 39 months from onset |

CPA, cyclophosphamide; CPT-11, irinotecan; DOD, died of disease; ETP, etoposide; IFO, ifosfamide; LN, lymph node; RTx, radiotherapy; TBI, total body irradiation; TMZ, temozolomide; VNR, vinorelbine; Zol, zoledronic acid.
progressive disease. She died of disease after ~1 year. In Patient 4, tumor sizes were stable for first 4 weeks. However, a new pleural metastasis lesion appeared at Day 28 and administration of sorafenib was discontinued due to progressive disease. She died of disease after 4 months.

Hypertension, diarrhea, skin rash, and increased AST/ALT were not observed in any patient.

Discussion

In this report, four patients with relapsed neuroblastoma were treated with sorafenib. This is the first report on sorafenib treatment for patients with neuroblastoma. Sorafenib showed minimal anti-tumor activity in our patients with refractory tumors. Our patients did not experience any sorafenib-related toxicity, during short administration period.

Anti-tumor activity in our patients was lost after a short stabilization phase. Sorafenib is approved for the treatment of advanced hepatocellular carcinoma by the US Food and Drug Administration. Sorafenib can inhibit hepatocellular carcinoma growth by three mechanisms: blocking tumor cell proliferation via the MAPK pathway; inducing apoptosis by reducing survival factors; and decreasing tumor angiogenesis by inactivation of PDGFR-β and VEGFR-2/3. However, many patients develop acquired resistance to sorafenib by various mechanisms including activation of the PI3K/AKT pathway, epithelial-mesenchymal transition, and autophagy [12, 13]. In neuroblastoma patients treated with sorafenib, the same mechanisms as for hepatocellular carcinoma might be involved in both the anti-tumor effect and the acquisition of resistance. Sorafenib might activate alternative survival pathway(s) in neuroblastoma cells. The combination of sorafenib with other agents targeting multiple survival pathways may be necessary to induce more sustained anti-tumor activity.

In summary, we report an experience of compassionate use of sorafenib in children with treatment-refractory neuroblastoma. While sorafenib showed minimal anti-tumor activity in our patients, it might still be effective in patients with neuroblastoma in an earlier stage.

Conflict of Interest

None declared.

References

1. Matthay, K. K., J. G. Villablanca, R. C. Seeger, D. O. Stram, R. E. Harris, N. K. Ramsay, et al. 1999. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. N. Engl. J. Med. 341:1165–1173.
2. Matthay, K. K., C. P. Reynolds, R. C. Seeger, H. Shimada, E. S. Adkins, D. Haas-Kogan, et al. 2009. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloblastic therapy followed by 13-cis-retinoic acid: a children's oncology group study. J. Clin. Oncol. 27:1007–1013.
3. Matthay, K. K., R. E. George, and A. L. Yu. 2012. Promising therapeutic targets in neuroblastoma. Clin. Cancer Res. 18:2740–2753.
4. Wilhelm, S., C. Carter, M. Lynch, T. Lowinger, J. Dumas, R. A. Smith, et al. 2006. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nat. Rev. Drug Discov. 5:835–844.
5. Chai, H., A. Z. Luo, P. Weersinghe, and R. E. Brown. 2010. Sorafenib downregulates ERK/Akt and STAT3 survival pathways and induces apoptosis in a human neuroblastoma cell line. Int. J. Clin. Exp. Pathol. 3:408–415.
6. Yang, F., V. Jove, R. Buettner, H. Xin, J. Wu, Y. Wang, et al. 2012. Sorafenib inhibits endogenous and IL-6/S1P induced JAK2-STAT3 signaling in human neuroblastoma, associated with growth suppression and apoptosis. Cancer Biol. Ther. 13:534–541.
7. Kakodkar, N. C., R. R. Peddinti, Y. Tian, L. J. Guerrero, A. Chlenski, Q. Yang, et al. 2012. Sorafenib inhibits neuroblastoma cell proliferation and signaling, blocks angiogenesis, and impairs tumor growth. Pediatr. Blood Cancer 59:642–647.
8. Navid, F., S. D. Baker, M. B. McCarville, C. F. Stewart, C. A. Billups, J. Wu, et al. 2013. Phase I and clinical pharmacology study of bevacizumab, sorafenib, and low-dose cyclophosphamide in children and young adults with refractory/recurrent solid tumors. Clin. Cancer Res. 19:236–246.
9. Inaba, H., J. E. Rubnitz, E. Coustan-Smith, L. Li, B. D. Furmanski, G. P. Mascara, et al. 2011. Phase I pharmacokinetic and pharmacodynamic study of the multikinase inhibitor sorafenib in combination with clofarabine and cytarabine in pediatric relapsed/refractory leukemia. J. Clin. Oncol. 29:3293–3300.
10. Widemann, B. C., A. Kim, E. Fox, S. Baruchel, P. C. Adamson, and A. M. Ingle. 2012. Glade Bender J, Burke M, Weigel B, Stempak D, Balis FM, Blaney SM. A phase I trial and pharmacokinetic study of sorafenib in children with refractory solid tumors or leukemias: a Children's Oncology Group Phase I Consortium report. Clin. Cancer Res. 18:6011–6022.
11. Kim, A., F. M. Balis, and B. C. Widemann. 2009. Sorafenib and sunitinib. Oncologist 14:800–805.
12. Gauthier, A., and M. Ho. 2013. Role of sorafenib in the treatment of advanced hepatocellular carcinoma: an update. Hepatol. Res. 43:147–154.
13. Chow, A. K., L. Ng, C. S. Lam, S. K. Wong, T. M. Wan, N. S. Cheng, et al. 2013. The enhanced metastatic potential of hepatocellular carcinoma (HCC) cells with sorafenib resistance. PLoS ONE 8:e78675.