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BRIEF REPORT

Retrospective experience of children with relapsed brain tumors treated with oral combination of axitinib and metronomic etoposide

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Abstract

Metronomic chemotherapy-based combinations have received interest for relapsed/refractory malignancies. Preclinical and clinical studies showed activity of metronomic etoposide and axitinib. We report our retrospective experience in six children treated with axitinib and metronomic etoposide for refractory/relapsed brain tumors as an "off-label" combination. Three patients with medulloblastoma experienced partial response; one patient with atypical teratoid rhabdoid tumor (ATRT) displays an ongoing stable disease (12 months); two patients with medulloblastoma had progressive disease. Grade 3–4 toxicities were observed in two patients (thrombocytopenia, anemia, diarrhea, fatigue). The axitinib–etoposide combination shows signals of efficacy in heavily pretreated patients with relapsed/refractory brain tumors. These results were based on real-world observation and will need formal evaluation in a phase I/II trial.

KEYWORDS
angiogenesis, ATRT, brain tumors, medulloblastoma, metronomic chemotherapy, VEGF

1 | INTRODUCTION

Pediatric central nervous system tumors (pCNS) are the second most common childhood malignancies and the most common cause of death among all childhood cancers.[1] There is currently limited available therapy for patients with relapsed medulloblastoma, ependymoma, and atypical teratoid rhabdoid tumor (ATRT). New strategies are needed for pediatric relapsed or refractory brain tumors.

Several metronomic chemotherapy (MC) regimens have shown activity in pCNS tumors,[2–4] raising interest for the different mechanisms of action of MC (inhibition of angiogenesis, immune regulation, direct cancer cells toxicity) and the sequential use of different agents to overcome drug resistance.[5] Recently, such a multidrug metronomic regimen called MEMMAT led to sustained complete remissions of 20% pediatric patients with medulloblastoma, who all previously underwent radiotherapy as part of their treatment.[6] These findings confirmed the results of previous retrospective studies for pCNS tumors.[6–8] Among MC agents successfully used in the MEMMAT protocol, etoposide appears as a clinically valid option for patients with medulloblastoma and ependymoma.[6] Several studies have described the clinical activity of metronomic etoposide in medulloblastoma and ependymoma.[9,10]

Axitinib is a second-generation tyrosine kinase inhibitor that works by selectively inhibiting vascular endothelial growth factor receptors (VEGFR-1/2/3). Through this mechanism of action, axitinib

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; MC, metronomic chemotherapy; OS, overall survival; pCNS tumors, pediatric central nervous system tumors; TEMIRI, temozolomide–irinotecan.

TABLE 1 Characteristics of the patients, treatments, and outcomes.

Patient' characteristics						
Age at diagnosis (years)	10 (months)	14	9	11	11	11
Sex	Male	Female	Female	Male	Female	Male
Type of disease	ATRT	Medulloblastoma	Medulloblastoma	Medulloblastoma	Medulloblastoma	Medulloblastoma
Molecular biology	/	No wnt, no shh, unamplified nmyc and cmyc, no group 3 or 4, positive EZH2	No wnt, no shh, unamplified nmyc, no group 3 or 4, 17p−, 14q+, 17q+	No wnt, no shh, unamplified nmyc, no group 3 or 4	No wnt, no shh, unamplified nmyc and cmyc, no group 3 or 4	Shh, amplified nmyc, X9q−, 10q−, 17p−
Previous Treatment						
- Nb of lines	8	3	8	3	3	6
- Surgery	All patients underwent surgery					
- Chemotherapy	All patients received chemotherapy					
- Immunotherapy	Nivolumab	–	–	–	–	–
- Targeted therapy	Bevacizumab	Bevacizumab	Bevacizumab, abemaciclib	Bevacizumab	Bevacizumab	Bevacizumab, vismodegib
- Metronomic chemotherapy	MEMMAT	MEMMAT, PROVIN	MEMMAT	MEMMAT	MEMMAT	MEMMAT
- Radiotherapy	All patients received radiotherapy					
Treatment pre-axitinib (best response; time on treatment in months)	ATRT09 (PR, 11) MEMMAT (PR, 24) Metronomic personalized[a] (PR, 8) METRO-PD1 (PR, 12)	SFOP2007 (RC, 4) PROVIN[b] (PD, 2) MEMMAT (PR, 13)	PNET HR (PD, 2) TOTEM (RC, 10) Metronomic MEMMAT (PR, 1) TEMIRI (PR, 3) Abemaciclib (PR, 3) METRO-PD1 (PR, 2)	SFOP2007 (RC, 4) TOTEM (PR, 14) MEMMAT (PR, 13)	PNET HR (RC, 24) TOTEM (PR, 2) MEMMAT (PR, 14)	PNET HR (RC, 12) MEMMAT (RC, 9) TOTEM (PR, 7)
Axitinib–etoposide treatment						
Age at treatment (years)	12	21	14	14	12	18
- Axitinib (mg/m^2/dose)	0.8	2.1	1.2	1.6	0.9	1.7
- Etoposide (mg/m^2/dose)	45	35	25	15	25	30
- Grade 3–4 adverse events	None	None	Grade 3: fatigue, diarrhea, anemia, thrombocytopenia	Grade 3: thrombocytopenia	None	None
- Grade 1–2 adverse events	Grade 1: fatigue, diarrhea, gingival pain, alopecia	None	Grade 2: high blood pressure, hypothyroidism	Grade 2: high blood pressure, diarrhea, proteinuria	Grade 1: fatigue	Grade 1: fatigue Grade 2: hypothyroidism
Best response	SD	PR	PR	PD	PD	Dissociated response
Duration of treatment (months)	8 (ongoing)	7	12	2	4	2
Treatment post-axitinib	/	None	None	METRO-PD1	SPARTO	None
Status at last follow-up (months)	AWD	DoD	DoD	DoD	AWD	DoD

Note: MEMMAT,[8] ATRT09,[23] METRO-PD1,[24] SFOP2007,[25] PNET HR.[26]

Abbreviations: AWD, alive with disease; DoD, died of disease; PD, progressive disease; PR, partial response; SD, stable disease; TEMIRI, temozolomide–irinotecan; TOTEM, topotecan and temodal.

[a]Tamoxifene, isotrétinoïne, etoposide, temodal.

[b]Oral metronomic vinorelbine, and propranolol.

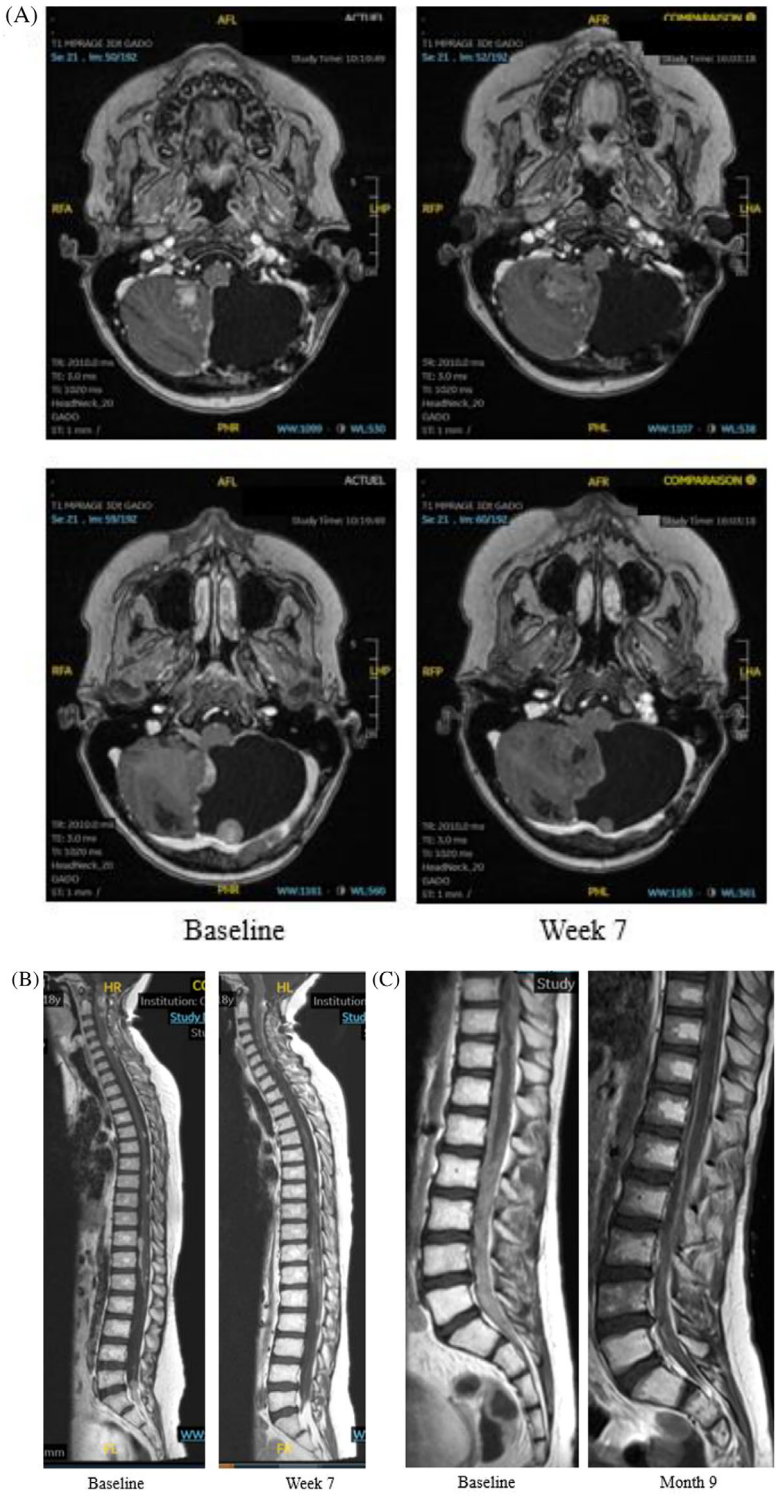

FIGURE 1 Examples of radiological response: MRI scan of patient illustrating response to treatment. Panel (A) • Baseline: Left lateral ventricle lesion 20 × 15 mm; lesion in left paramedian posterior cerebral fossa 13 mm; right acousticofacial bundle lesion 12 × 10 mm; fornix lesion 25 × 32 mm; right cerebellar lesion 20 × 19 mm; optic chiasma lesion; ventricular volume diameter 24 mm; Left corpus callosum splenium lesion 18 × 23 mm. • Week 7: (i) Decreased: left lateral ventricle lesion 18 × 12 mm; left paramedian posterior cerebral fossa lesion 7 mm; bilateral acousticofacial bundle lesions; cervical lesions. (ii) Increased: fornix lesion 40 × 28 mm; right cerebellar lesion 43 × 33 mm; optic chiasma lesion; left ventricular subependymal leptomeningeal lesion; ventricular volume diameter 36 mm. (iii) Stability: perimedullary lesions. Panel (B) • Baseline: Leptomeningeal lesion C1 20 × 15 mm and L5-S1 (with mass effect). • Week 7: (i) Decreased: cervical lesions. (ii) Stability: perimedullary lesions.

may block tumoral angiogenesis, tumor growth, and metastases.[11] Preclinical studies showed activity of axitinib in medulloblastomas and in ependymomas.[12–14]

In the context of hard-to-cure relapsed or refractory pCNS tumors, we used an "off-label" regimen of oral etoposide and axitinib in three tertiary institutions. We report real-world data through a retrospective case series.

2 | METHODS

We retrospectively collected and analyzed data from patients aged 0–21 years treated in three pediatric oncology units in France from January 2022 to December 2023 who received oral axitinib and metronomic etoposide. All patients had relapsed or refractory brain tumors.

Treatment consisted of an oral regimen of axitinib given twice a day in combination with once daily oral etoposide. Both drugs were given on a continuous basis. Recommended dose of axitinib used as single agent after the phase 1 trial in children was 2.4 mg/m^2/dose twice a day, which led to PK exposures similar to those of adults.[15] Metronomic etoposide is usually given at the dose of 50 mg/m^2/day.[16,17] Different dosages were given based on the number and type of previous lines of treatment and their tolerance according to responsible physician.

Demographic and medical (including laboratory tests and imaging such as magnetic resonance imaging [MRI] scans) data were collected from the electronic medical charts of patients. Cerebral and spinal MRI (T1- and T2-weighted sequences) were repeated at least every 2–3 months during treatment and during follow-up until progression. Progression-free survival (PFS) and overall survival (OS) were defined as time from initiation of treatment to date of relapse or progression or death from any cause. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. Bloodwork. The modalities of follow-up were defined by the responsible physician.

Patients were treated "off-label" under their physician responsibility and after information on "off-label" prescriptions. Ethics approval was granted for retrospective analysis of data by the ethics committee from local Ethics Review Board: Assistance Publique des Hôpitaux de Marseille—CSE 2349-November 2023.

3 | RESULTS

Six patients (three males, three females) with a median age of 11 years [7; 11.7] at diagnosis were included in this analysis. They received the axitinib–etoposide combination in three pediatric oncology units. Characteristics of the patients, treatments, and outcomes are detailed in Table 1. All patients had metastatic relapsed or refractory central nervous system (CNS) brain tumors (five medulloblastomas and one ATRT). All patients previously received a median number of 4.5 (range 3–8) lines of therapy, including chemotherapy, radiotherapy, and surgery prior to receiving axitinib–etoposide combination.

Modalities and response to axitinib–etoposide combination are detailed in Table 1. Examples of radiological response are illustrated in Figure 1. Median age at the time of treatment was 14 years [12–19], and median time from diagnosis to MC treatment was 70 months [48–101]. Dose of axitinib ranged between 0.8 and 2.1 mg/m^2/dose taken twice a day, and dose of etoposide ranged between 15 and 45 mg/m^2/day. Five grade 3 and 4 toxicities were reported in two patients. One case of grade 2 high blood pressure was reported, treated with calcic antagonist. Treatment had to be temporarily suspended due to grade 3 diarrhea in one patient. Dose reduction was necessary for two patients (one for diarrhea, one for thrombocytemia). Best responses were partial responses (3), stable disease (1), while two progressive diseases were also observed. Overall, at last follow-up four deaths were reported, one patient with medulloblastoma switched to new treatments and is alive at 6 months and one patient with ATRT is still under treatment after 12 months.

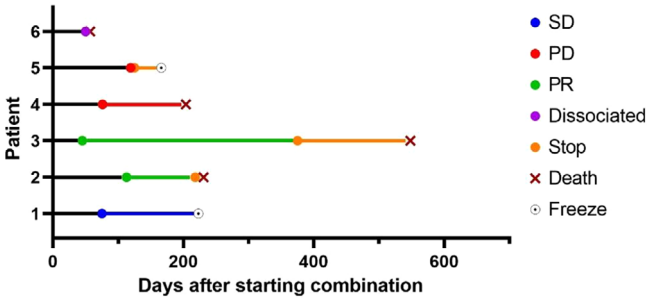

FIGURE 2 Swimmer plot. freeze, data freeze; PD, progressive disease; PR, partial response; SD, stable disease.

4 | DISCUSSION

In this retrospective experience, we report real-word data of the "off-label" treatment with axitinib and metronomic etoposide in six children or adolescents with pediatric relapsed/refractory metastatic brain tumors (Figure 2) three patients with medulloblastoma experienced partial response or dissociated response and one patient with ATRT has an ongoing stable disease on treatment.

The observed clinical and radiological responses to axitinib–etoposide appear promising in these patients who have progressed despite several lines of treatment, including radiotherapy. This is consistent with the preclinical studies of axitinib that have shown activity in medulloblastoma in vitro and in vivo alone or when combined with metronomic etoposide[13] or gemcitabine.[14] Potential activity has also been reported in ependymoma,[18] but no patients with ependymoma have been treated with this combination. These results are consistent with previous preclinical data that have reported synergy between MC and drugs targeting VEGF,[19,20] further illustrated by responses seen in the MEMMAT and the temozolomide–irinotecan (TEMIRI) plus bevacizumab combinations.[6,21] However, it is difficult to discriminate the respective contribution of axitinib or etoposide. Oral metronomic etoposide was shown to provide prolonged clinical benefit in patients. However, these are older studies, with different prior treatments and fewer lines of therapy.[6,21]

All patients reported here had previously received one line of MC and bevacizumab. This suggests that there is a potential for rechallenging heavily pretreated patients with MC and anti-VEGF agents.[22,23] Some patients were treated according to the MEMMAT protocol before receiving the axitinib–etoposide combination, with a partial response despite the previous use of an anti-VEGF and etoposide in both cases. We can assume that there is no systematic cross-resistance with MC and/or with anti-VEGF monoclonal antibody, likely for the later due to the use of a pan-VEGF inhibitor peptide.

So far, axitinib–etoposide showed a limited number of grade 3–4 hematological toxicities. Diarrhea and hypertension were previously reported in the phase 1 trial by Geller et al.[22] Of note, these toxicities seemed to occur in patients in whom lower dose of etoposide was used likely reflecting anticipated toxicity based on tolerance of previous lines of treatment. Furthermore, this "all-oral" treatment shall be advantageous over bevacizumab in terms of quality of life, as the oral

formulation facilitates administration, allowing treatment to be taken at home.

5 | CONCLUSION

The oral combination of axitinib and metronomic etoposide appears promising with three responses and one sustained stable disease among six patients with relapsed/refractory medulloblastoma or ATRT after failure of radiotherapy. Three hematological and one digestive grade 3–4 toxicities were observed. These real-word data further strengthen the preclinical rationale, and the implementation of a formal phase 1 clinical trial is planned to determine the recommended dose for phase 2 of the combination treatment and further explore its clinical activity in pCNS tumors and its role compared to MEMMAT or bevacizumab-TEMIRI.

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CONFLICT OF INTEREST STATEMENT

Caroline Donzé, Gabriel Revon-Rivière, Arnauld Verschuur, and Morgane Pondrom have no conflicts of interest to disclose. Nicolas André has had an advisory role for Bayer, Alexion, Partners Therapeutics, and receives grants (institution) from Bristol Myers Squibb and drugs for a trial from Bristol Myers Squibb, Pierre Fabre, Merck, Pfizer, and travel support from Roche, Novartis, Alexion; he further has IDMC roles for Accord Healthcare. He also received funding for Region SUD, Gouvernement de Monaco, AMIDEX, La Ligue contre le Cancer, and Fondation Flavien for a phase 1/2 evaluating axitinib. Pierre Leblond reports receiving support from Merck Serono (Cilent study), BMS (Metro-PD1 study), Pierre-Fabre (Ovima study), and Alexion (Selumetinib board).

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