MEDICAL UNIVERSITY OF VIENNA

MEMMAT - A Phase II study of metronomic and targeted anti-angiogenesis therapy for children with recurrent/progressive medulloblastoma

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Introduction

Patients with recurrent medulloblastoma have a poor prognosis, irrespective of therapy used, including surgery, conventional chemotherapy, re-irradiation, and high-dose chemotherapy. An alternative approach is an antiangiogenic metronomic combination therapy that inhibits multiple pro-angiogenic pathways targeting non-overlapping aspects of neovascularization and exerting its effect on the microenvironment to overcome treatment resistance.

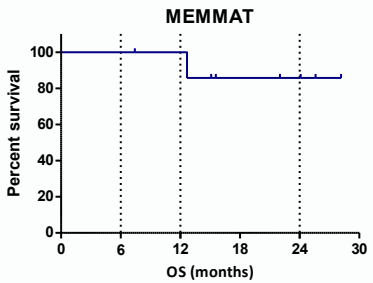
Patients and Methods

We present an international phase II study intended to include 40 patients with recurrent or progressive medulloblastoma who will be treated with a metronomic antiangiogenic regimen (MEMMAT; ClinicalTrials.gov Identifier: NCT01356290).
Treatment consists of bevacizumab infusion every two weeks, continuous oral celecoxib, thalidomide, and fenofibrate, with alternating 21-day cycles of low-dose cyclophosphamide and etoposide, as well as intraventricular therapy with etoposide and liposomal cytarabine. Primary endpoint is the response rate 6 months after start of antiangiogenic treatment. Secondary endpoints are overall survival (OS), progression free survival (PFS), toxicity, quality of life, performance status, and prognostic factors.

Results

The first patient was recruited in April 2014, study completion is expected in 2020. To date, 10 patients between 6 and 15 years (mean age 10 years) were enrolled. Seven of the patients were first recurrences, two suffered from their third recurrence.
No major unexpected toxicities and no treatment related deaths were reported. To date, 9/10 patients are still alive.

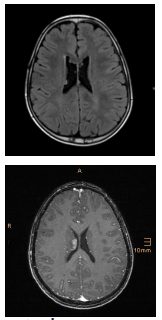
Figure 1. MEMMAT: OS survival



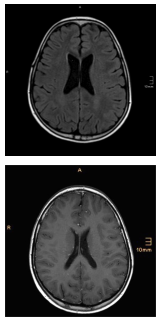
Case, sex	Age at diagnosis (years)	Sub-Group	Primary therapy (RTX/ CTX)	Number of relapse	Type of relapse	Age at MEMMAT start (years)	Duration of MEMMAT (months)	Response after 6 months	Treatment in addition to MEMMAT after 6 months	Status/ Follow-Up (months)
Vienna										
1, m	11	4	+/+	1	M3	15	24	CR	-	CR, 30
2, m	7	n.a.	+/+	1	M2	9	24	CR	-	CR, 28
3, f	7	4	+/+	3	M2	9	26	CR	Gamma Knife (2x) **	PR**, 26
4, m	9	n.a.	+/+	1	M2	11	24	PR	local RTX	PR, 24
5, f	11	(3) no medullo ?	+/+	1	M3	11	2	PD	-	DOD, 13
6, f	8	4	+/+	1	M3	9	3	PD	-	SD, 15
7, m	6	n.a.	+/+	3	M2/M3	9	9	PR	-	PR, 9
Boston										
1, m	7	n.a.	+/+	1	local	8	17	CR	-	CR, 18
2, f	n.a.	n.a.	+/+	1	n.a.	14	2	*	-	*, 2
Brno										
1, m	5	n.a.	+/+	1	M2	6	3	*	-	*, 4

* too early to evaluate; ** new metastasis 20 months after start of MEMMAT, Gamma Knife additional to MEMMAT

Figure 2. Patients 2 and 4 (Vienna)



at relapse



6 months after start of MEMMAT

Conclusion

The preliminary results suggest that the MEMMAT regimen has promising clinical activity in recurrent medulloblastoma.