

# Radiation Therapy and Concurrent Topotecan Followed by Maintenance Triple Anti-Angiogenic Therapy With Thalidomide, Etoposide, and Celecoxib for Pediatric Diffuse Intrinsic Pontine Glioma

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**Background.** Despite major treatment attempts, the prognosis for pediatric diffuse intrinsic pontine gliomas (DIPGs) remains dismal. Gliomas are highly vascularized tumors, suggesting that the prevention of vessel formation by anti-angiogenic treatment might be effective. **Procedure.** Forty-one pediatric patients with DIPG were treated according to the Angiocomb protocol, starting with radiotherapy combined with topotecan and followed by anti-angiogenic triple medication consisting of thalidomide, etoposide, and celecoxib. Overall survival, radiological response, quality of life, requirement of corticosteroids, and adverse effects were monitored. Eight patients treated with only radiotherapy were used as controls. **Results.** For study patients, the 12 and 24 months overall survival was

61% and 17%, respectively. The median overall survival was 12 months (range 4–60 months). Four radiological complete responses were seen, of which two were transient. Radiologically, 56% of the tumors reduced in size and 78% in signal intensity. Study patients were able to visit school or daycare and walk for a significantly longer time compared to controls (Log Rank 0.036 and 0.008, respectively). Adverse effects were generally minor. **Conclusions.** The Angiocomb protocol created a noticeable share of long-term survivors and was well tolerated, suggesting that anti-angiogenic therapy for patients with DIPG should be studied more in the future. *Pediatr Blood Cancer* © 2014 Wiley Periodicals, Inc.

**Key words:** anti-angiogenic therapy; celecoxib; etoposide; pediatric; pontine glioma; thalidomide

## INTRODUCTION

Brain tumors are the most common solid malignancies of childhood [1]. Twenty percent arise from the brainstem, and of these, diffuse intrinsic pontine gliomas (DIPGs) account for the largest share [2]. Despite major treatment attempts, the prognosis for DIPG still remains poor and most patients die within a year of diagnosis [2].

Gliomas are known to be densely vascularized tumors and very dependent on angiogenesis [1,3]. Suppression of blood vessel growth by anti-angiogenic drugs might therefore be effective in the treatment of DIPGs. In addition to being important for tumor growth, blood vessels also give rise to drug resistance [4], since the blood–brain barrier prevents chemotherapeutic agents from penetrating from the bloodstream to the site of action [4–6]. Anti-angiogenic treatment targets the tumor vessel walls and does not require penetration of the blood–brain barrier [7]. Angiogenesis can be inhibited by metronomic administration of drugs, meaning oral, long-lasting dosing without breaks [8–10].

From these findings, the Angiocomb protocol for treatment of brainstem gliomas was developed. Preliminary results from the Angiocomb pilot study were encouraging: the overall survival (OS) 12 months from diagnosis was 63% and the quality of life was remarkably better compared to controls treated with only radiotherapy [11].

## PATIENTS AND METHODS

### Patients

Altogether 45 patients with DIPG were recruited consecutively in 13 centers in all five Nordic countries. From this group, two patients treated with only radiotherapy and topotecan were included

in the analysis of the topotecan effect and toxicity but excluded from the other analyses. One patient with DIPG both radiologically and histologically treated according to the Angiocomb protocol was excluded from all analyses due to an atypical clinical picture prior to diagnosis. This patient is included in the adverse effect report.

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One patient had a troublesome disease, complicated by central venous catheter derived sepsis, deep vein thromboses, and recurrent convulsions during the radiotherapy, resulting in a break in radiotherapy and topotecan treatment and death before the initiation of the triple medication. This patient has been excluded from all analyses. Forty-one patients were included in the final analysis (Table I). None of the patients had NF-1. In addition to the 41 patients with DIPG, two patients with primarily thalamic tumors later disseminating to the brainstem treated according to the Angiocomb protocol are included when reporting adverse effects but excluded from all other analyses.

## Controls

Eight controls, diagnosed and treated with only radiotherapy at Helsinki University Central Hospital, were identified (Table I). It was difficult to find eligible control patients since different DIPG trials have been going on over the years in the Nordic countries. All controls participated in the pilot study [11].

## Treatment

The Angiocomb protocol for treatment of DIPGs was developed at the Children's Hospital, University of Helsinki, Finland. The treatment started with local radiotherapy. Patients received a dose of 54–60 Gy in 1.8 Gy fractions. Three patients received 31.8–50.4 Gy: one patient wanted to discontinue radiotherapy in advance, one patient received a smaller dose due to his young age and one patient a reduced dose since the tumor was located partly in medulla oblongata. Decisions to reduce the radiation dose were made by the patients' physicians. The controls received 50–60 Gy. The median dose for both study patients and controls was 54 Gy. Topotecan, a topoisomerase I inhibitor, was used as a radiosensitizer and was

given as a 30–60 minutes intravenous infusion before each radiotherapy session with a dose of 0.5 mg/m<sup>2</sup> to all patients. The controls did not receive topotecan.

The triple medication consisting of oral thalidomide (1–6 mg/kg/day), oral or intravenous etoposide (20–70 mg/m<sup>2</sup>/day as oral dose) and oral celecoxib (230 mg/m<sup>2</sup>/day for older patients and 7 mg/kg/day for the younger ones) were started 4 weeks after completion of radiotherapy. Six patients received intravenous etoposide twice weekly due to lack of oral preparation at that time. In cases where etoposide was administered intravenously, doses were recalculated to corresponding oral doses by using a bioavailability of 40% (Professor S. Eksborg, Karolinska University Hospital, Sweden, personal communication, Supplemental Information). Thalidomide and etoposide doses were titrated according to adverse effects like neutropenia. The median dose was 2.2 mg/kg/day for thalidomide (30/41 patients) and 30 mg/m<sup>2</sup>/day for etoposide (26/41 patients). Drugs were paused only during severe neutropenia, infections, or other adverse effects. Median number of pause days was seven for both thalidomide and etoposide. Corticosteroid therapy was recorded and sulfa-trimethoprim prophylaxis recommended.

Nine patients received second line treatment after Angiocomb due to disease progression. From this group, two patients got additional third line treatment, one patient third and fourth line treatments and one patient a fifth line therapy.

Time of diagnosis was defined as the date of the first brain MRI. Clinical data were collected from patient charts from diagnosis until death. Since the data were collected retrospectively, all information could not always be retrieved. In brackets we report the number of patients with information available in relation to the number of patients included in the whole group.

Recruitment ended on January 1, 2013, and for those patients still alive, follow-up ended on May 1st, 2013. In cases of clinical and radiological stable or responsive disease, medication was continued. In cases of MRI progression, continuation of medication was decided based on the adverse effects of the therapy and the clinical status of the patient. Absolute indications for discontinuation of the medication were wish of the patient or family, decreased level of consciousness, and inability to swallow.

## Response Evaluation

Therapy response was assessed based on follow-up of the clinical status and MRI findings. Brain MRI was recommended to be performed at diagnosis, 4 weeks after discontinuation of radiotherapy, and thereafter every three months. There was no systematic imaging follow-up for controls. Controls without MRI images at diagnosis (N = 1; only CT images available) or follow up MRIs (N = 2) could not be used when assessing the radiological response. We chose to register three MRI parameters during therapy: (1) tumor size, (2) signal intensity on T2-weighted images, considered to be a marker for tumor edema [12], and (3) spread of tumor to the surrounding tissues. Changes in tumor size and signal intensity were registered on a three-step scale (stable, progression, and response). In those cases where the tumor was measurable, a change in diameter with >1 cm in the axial plane was regarded significant. Spread of the tumor was classified as either present or absent. The effect of radiotherapy and topotecan was assessed by comparing the diagnostic MRI with the first follow-up image about 3 months after the diagnosis. For assessment of the effect of the

**TABLE I. Characteristics of Patients and Controls**

	Patients	Controls
Number of patients	41	8
Country		
Finland	16	8
Sweden	12	0
Denmark	7	0
Norway	4	0
Iceland	2	0
Male/female	16/25	4/4
Median age at diagnosis (year)	6	7.5
Age range (year)	1–16	5–15
Biopsy at diagnosis (N)	11	6
Tumor grading at diagnostic biopsy (N)		
Grade I <sup>a</sup>	1	0
Grade II	4	1
Grade III	5	4
Grade IV	1	1
Tumor grading at autopsy (N)		
Grade I	0	0
Grade II	2	0
Grade III	0	0
Grade IV	4	0

<sup>a</sup>One patient had a grade I atypical pilocytic astrocytoma, but the biopsy was very small and probably not representative for the whole tumor. Clinically and in MRI the tumor behaved like a typical DIPG.

triple medication, each follow up MRI was compared to the MRI taken about 3 months earlier.

The effect of the triple medication was evaluated based on four other parameters: overall survival, quality of life, requirement of corticosteroids and adverse effects. Quality of life was assessed based on (1) how long patients were able to attend school or daycare; (2) time to requirement of wheelchair; and (3) start date for need of strong opioids, either consistently or on demand.

**Statistical Analysis**

The data were analyzed with IBM SPSS Statistics Version 20 (SPSS, Chicago, IL). Mann–Whitney *U*-Test, Kaplan–Meier Survival analyses and Log Rank tests were utilized. The study was approved by the Institutional Review Board of the P.I. centre (Helsinki) and informed consent was obtained from the parents and age-appropriate patients. The Angiocomb protocol has been registered at ClinicalTrials (identification number: NCT01756989).

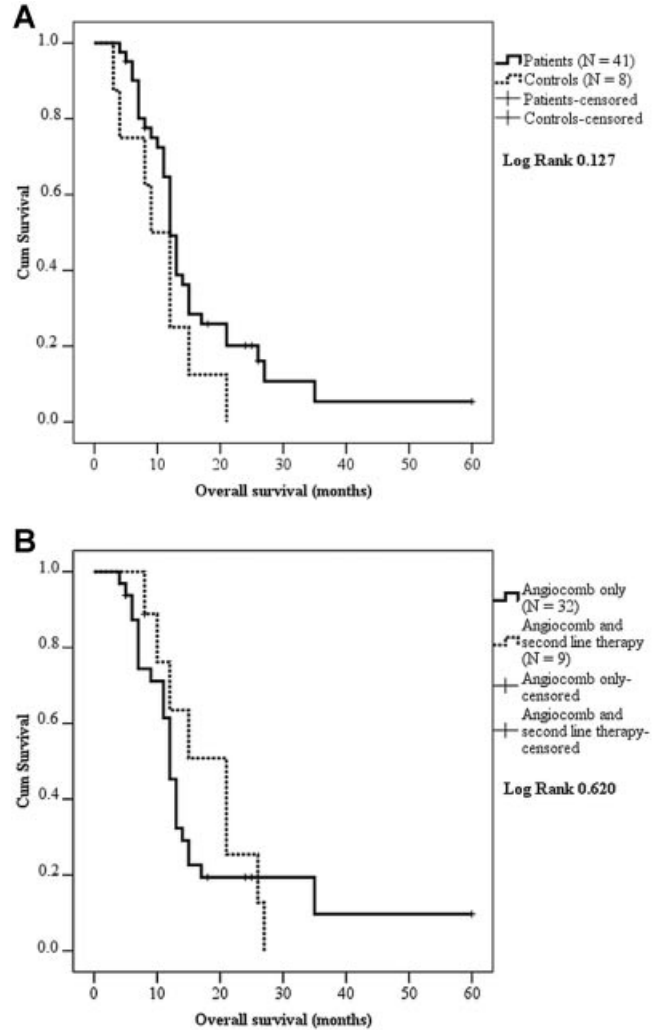
**RESULTS**

**Overall Survival**

The median overall survival (OS) for patients treated with Angiocomb (N = 41) was 12 months (range 4–60 months) and for controls 10.5 months (N = 8, range 3–21 months). There was no statistical difference in the overall survival between patients and controls (Log Rank 0.127; Fig. 1A), or in the OS between patients with triple medication only (N = 32) and patients with second line therapy (N = 9; Log Rank 0.620; Fig. 1B). The OS 12 months from diagnosis was 61% for patients treated with Angiocomb (25/41) and 50% (4/8) for controls. Eight patients were alive at the end of follow-up.

**Long-Term Survivors**

Seven out of 41 patients treated with Angiocomb (17%) were long-term survivors (OS ≥ 24 months; Table II). The median OS in this group was 26 months (range 24–60 months, mean 32 months). All of them had typical radiological findings at diagnosis and typical DIPG symptoms, although one patient had a long duration of symptoms (about 18 months) prior to diagnosis. Neither thalidomide nor etoposide doses differed between long-term survivors and other patients treated with Angiocomb. None of the controls survived over 24 months. The patient with longest survival, a girl diagnosed with histologically verified grade II–III glioma at the age of 13, had at the end of follow-up an OS of 60 months. The triple



**Fig. 1.** Overall survival of (A) patients treated with Angiocomb and controls; (B) patients treated with only triple medication and patients with additional second line therapy.

medication was discontinued after 54 months, and she is presently neurologically asymptomatic and living a normal life. Her tumor size has been stable during the treatment. In addition, one patient with a grade II astrocytoma treated according to the Angiocomb protocol but excluded from analyses due to atypical DIPG

**TABLE II. Characteristics of Long-Term Survivors (Overall Survival >24 Months)**

Patient	Age <sup>a</sup> (years)	Survival (months)	Duration of Angiocomb (months)	Tumor grade	Response to RT and topotecan	Second line therapy	Dead/alive
1	13	60	54	II–III	Stable size, signal intensity reduced	No	Alive
2	3	35	30	No biopsy	Reduction in size and signal intensity	No	Dead <sup>b</sup>
3	12	27	9	No biopsy	Stable size, signal intensity reduced	Yes	Dead <sup>b</sup>
4	3	26	20	No biopsy	Reduction in size and signal intensity	Yes	Dead <sup>b</sup>
5	1	26	On medication	No biopsy	MRI missing <sup>c</sup>	No	Alive
6	9	24	11	No biopsy	Stable size, signal intensity reduced	No	Alive
7	11	25	13	II	Stable size, signal intensity reduced	No	Alive

RT, radiotherapy. <sup>a</sup>At diagnosis. <sup>b</sup>No autopsy. <sup>c</sup>Complete response on MRI 30 months after diagnosis.

symptoms at diagnosis had at the end of follow-up survived for 53 months.

### MRI Review

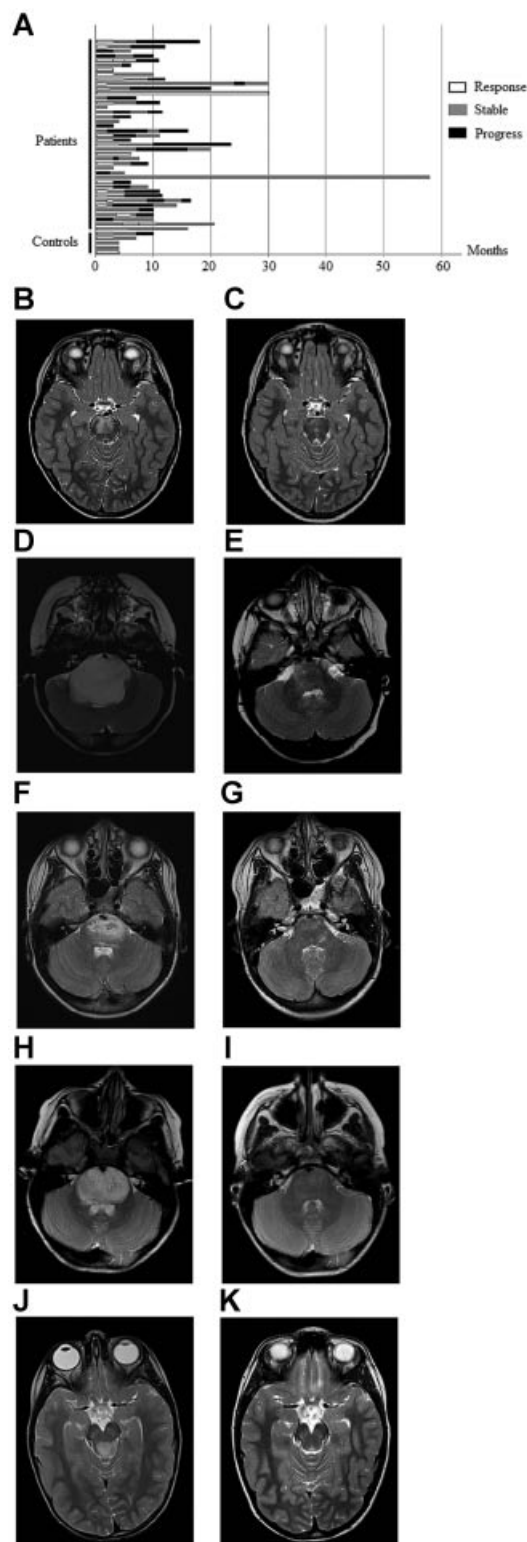
MRI images of all patients, including two patients treated with only radiotherapy and topotecan, were re-analyzed by the central reviewer to confirm the diagnosis and response. Changes in signal intensity were not evaluable in images of one patient and three controls. The effect of radiotherapy and topotecan was not evaluable for one study patient since the MRI was missing. After radiotherapy and concomitant topotecan treatment, 50% of the patients (21/42) had a size reduction of the tumor and 66% (27/41) had reduction in signal intensity. During triple therapy, 12% of the patients (5/41) had an additional reduction in tumor size and 30% (12/40) an additional reduction in signal intensity. Altogether, 56% (23/41) had a radiological response in tumor size at any time during the follow-up (Fig. 2A) and 78% (31/40) had reduction in signal intensity. Forty-three percent (17/41) had spread of the tumor to surrounding tissues in median 9 months after diagnosis. Out of five controls, two (40%) had reduction in tumor size and signal intensity during the radiotherapy. Due to the small number of controls, it was not possible to make any statistical analysis to determine the effect of topotecan.

Radiologically, there were four complete responses among study patients (Table III), of which two were transient. In the first case, the tumor (grade II astrocytoma) disappeared completely in the MRI taken after radiotherapy 5.5 months after diagnosis (Fig. 2B and C). MRIs performed 9, 12, and 16 months after diagnosis confirmed this complete response. The second patient had a tumor sized 4.6 cm × 4.9 cm in the diagnostic MRI. 30 months after this, the only sign of the tumor was a minimal area of increased signal (Fig. 2D and E). The third patient had only an insignificant area of enhancement left after radiotherapy (Fig. 2F and G) 2.5 months after diagnosis. Unfortunately the tumor started to grow 10 months after diagnosis. The fourth patient had also a transient complete response; the tumor had disappeared completely in the MRIs taken 3 and 7 months after diagnosis (Fig. 2H and I). Radiologically progression was seen 11 months after diagnosis. None of these patients underwent a partial resection of the tumor. One patient treated according to the Angiocomb protocol but not included in the study due to atypical symptoms has a sustained complete response radiologically (Fig. 2J and K).

### Quality of Life

The quality of life has been excellent for most patients treated with Angiocomb. Many have been able to do sports, travel and live an almost normal life. Seventy-five percent of the patients (24/32) were able to visit school or daycare. The median length of attendance to school or daycare was 9 months after the diagnosis (range 0–60 months) for patients treated with Angiocomb, which was significantly longer compared to controls (Log Rank 0.036). The corresponding number for controls was 63% (5/8; median 4 months, range 0–11 months; Fig. 3A).

Eighty-three percent of the patients (30/36) required wheelchair at a median of 9 months after diagnosis (range 0–32 months). All controls required wheelchair at a median of 3 months after the diagnosis (range 0–11 months). The median time to requirement of wheelchair was significantly longer among patients treated with Angiocomb compared to controls (Log Rank 0.008; Fig. 3B).



**Fig. 2.** (A) Responses in tumor size for patients treated with Angiocomb (N = 41) and controls (N = 5). MRI for (B) patient 1 at diagnosis; (C) patient 1: 16 months after diagnosis; (D) patient 2 at diagnosis; (E) patient 2: 30 months after diagnosis; (F) patient 3 at diagnosis; (G) patient 3: 2.5 months after diagnosis; (H) patient 4 at diagnosis; (I) patient 4: 7 months after diagnosis; (J) patient 5 at diagnosis; (K) patient 5: 50 months after diagnosis.

TABLE III. Characteristics of Patients With Radiological Complete Responses

Patient	1	2	3	4
Age at diagnosis	4	1	12	5
Tumor grade at diagnosis	II	No biopsy	No biopsy	No biopsy
OS at end of follow-up (months)	18	26	14	21
Current status	Alive	Alive	Dead	Dead
Clinical progression <sup>a</sup> (months)	No	No	10/11	—/19
First radiological progression (months)	No	No	10	11
Triple therapy length (months)	Ongoing	Ongoing	12	6
Reason for ending triple therapy	Ongoing	Ongoing	Progression	Progression and parents' wish
Second line therapy	No	No	No	Yes
Requirement of corticosteroids <sup>b</sup>	0%	0%	5.4%	Missing

<sup>a</sup>Attendance to school or daycare and start for requirement of wheelchair (months after diagnosis). <sup>b</sup>Share of days after diagnosis with corticosteroid intake. Median for all AngioComb patients was 23%.

Sixty-three percent of patients (22/35) and all controls with information available (6/8) needed strong opioids. The median time for start of opioids was 13 days before death among study patients (range 0–148 days) and 47 days among controls (range 0–121 days;  $P=0.183$ ). Study patients were treated with corticosteroids in

median 23% of the follow-up (range 0–100%,  $N=32/41$ ), controls 66% of the survival time (range 11–98%;  $N=7/8$ ) ( $P=0.115$ ).

### Toxicity

All brainstem biopsies were performed without mortality or clinical deterioration. Adverse effects of radiotherapy with topotecan and triple therapy were collected from 42 and 38 patients, respectively. In general, the tolerability of both topotecan and triple medication was good. Nine out of 42 patients had pauses in the administration of topotecan for a median of 8 days (range 1–14 days) and additionally 3/42 patients required a transient reduction of the topotecan dose due to grade III–IV neutropenia (12/42 patients; 29%). In addition to neutropenia, 28% (11/39) of the patients required blood transfusion due to anemia and 13% (5/39) due to thrombocytopenia. One patient had a shunt infection and one patient febrile neutropenia.

All patients except two (95%; 36/38) had some side effects of the triple therapy, in general minor. Seventy-four percent of the patients (28/38) were neutropenic during triple medication (grade III, 6/24 patients and grade IV, 17/24 patients), 8/38 patients (21%) suffered from anemia (grade III, 0 patients and grade IV, 1 patient), and 1/38 (2.6%) from grade IV thrombocytopenia. Fifty-three percent (20/38) had infections (grade III, 16 patients and grade IV, 1 patient), of which sepsis (11/38), and pneumonia (13/38) were the most common ones. Eighteen percent (7/38) had mild neuropathy and 16% (6/38) skin problems (exfoliating dermatitis and erythema of palms and soles; nostril and mouth ulcers, skin infections). Intratumoral hemorrhage, elevated liver enzymes and hypertension were seen in one case each. General symptoms such as tiredness, vomiting, nausea and epileptic seizures, which could be caused by both the disease itself and AngioComb medication were not listed.

Seventy-seven percent of the patients (23/30) were able to use thalidomide and 85% (22/26) etoposide with the recommended dosage. Among patients that have ended the treatment, the median length of the triple medication was 7 months (range 1–54 months;  $N=36/41$ ). The most common reason for ending the medication was disease progression (25/34; 74% of patients).

### DISCUSSION

We studied the effect of radiotherapy with concomitant topotecan followed by a metronomic anti-angiogenic combination

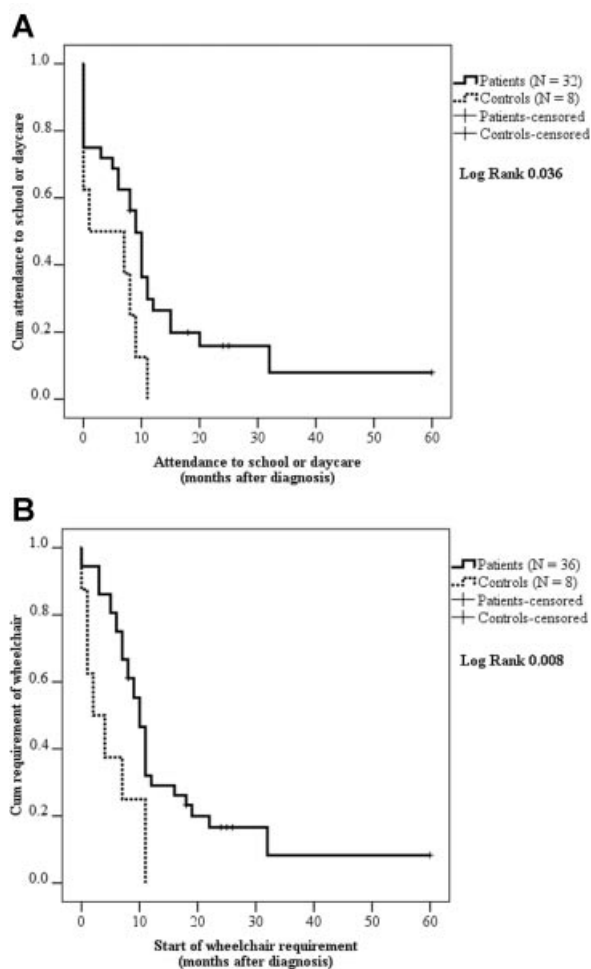


Fig. 3. (A) Attendance to school or daycare among patients treated with AngioComb and controls; (B) start of requirement of wheelchair among patients treated with AngioComb and controls.

therapy of thalidomide, etoposide, and celecoxib in the treatment of pediatric patients with DIPGs. Patients treated with Angiocomb achieved a good overall survival for this disease, with 17% of the patients surviving over 24 months. Radiologically, 56% of the patients had a reduction in tumor size and 78% a reduction in signal intensity during the treatment. Four complete responses, of which two were transient, were seen. Study patients were able to visit school or daycare and walk for a significantly longer time compared to controls. Side effects were generally mild.

In our study, the median OS was 12 months. The OS at 12 months was 61% and at 24 months 17%. In previous studies patients with DIPG have obtained a median OS of 8–11 months, a 12 months OS of 20–50% [7,13,14], and 24 months OS of 3–20% [2,14]. Only a few protocols have reached better results [15–17]. Finding controls treated with radiotherapy only is a general problem, since most patients have received chemotherapy as a part of different clinical trials and cannot be utilized as controls. Previous studies have reported median OS for patients treated with only radiotherapy to be 9–12 months [18,19]. There was no statistical difference in the survival between patients treated with Angiocomb and controls, although it cannot be excluded that the small number of controls and their relatively good OS (10.5 months) may have influenced the results. Which part of the treatment—the radiotherapy, topotecan or the metronomic drugs—had the most significant impact on the outcome is impossible to determine.

In total, 17% of the study patients were long-term survivors (OS  $\geq$  24 months, median 26 months, mean 32 months) with typical clinical findings. In this group, all patients except for one had also a short history of symptoms. Whether these patients had something in common, making them more receptive to the anti-angiogenic therapy, needs further studies. They might belong to the DIPG subgroup in which pro-angiogenic pathways characterized by up-regulation of genes associated with angiogenesis and endothelial cell proliferation are critical for tumor development [20]. The tumors of two patients with an OS of 25 and 60 months were histologically assessed to be grade II and II–III, respectively, which may have an influence on the survival and positively bias the results.

Topotecan converts partial, reversible breaks in the chromosomes of the malignant cells to total, irreversible splits in the DNA strand, thus enhancing the effect of radiotherapy [21]. Topotecan studies have previously yielded conflicting results [21,22]. Unfortunately, it was not possible to determine its effect in our study due to lack of suitable controls.

In DIPGs, the clinical state of the patient and radiological responses in conventional MRIs are known to have a weak correlation [23]. No generally accepted criteria for assessing the radiological response exists [7]. Two sustained and two transient complete responses in addition to one sustained complete response for a patient not included in the study were seen.

Almost all earlier studies concerning DIPG therapy have focused on survival of the patient alone. In our study, we also investigated the effect of the therapy on the quality of life. Measuring quality of life is complex in many ways. We chose to measure three parameters that were as objectively and easily defined as possible: the length of the time that the patients could visit school or daycare, the time to consistent need of wheelchair and the time to the need of strong pain relievers. Going to school or daycare is important for pediatric patients, and both requirement of wheelchair and need for strong pain relief is a possible sign of

disease progression. In our study, patients were able to attend school or daycare and walk for a longer period of time after diagnosis than the controls. Patients were treated in ambulatory fashion with oral drugs, so they could spend all the time at home instead of hospital.

The amount of adverse effects is also a way to measure the quality of life. The Angiocomb protocol was generally well tolerated, with the main adverse effects being neutropenia and infections. It is noteworthy that most of the patients also received corticosteroids. The tumor itself can also give rise to symptoms that may be misinterpreted as adverse effects. One of the main reasons for the good tolerability of the therapy was possibly the low dosing of the drugs.

There are certain limitations to this study. A larger number of controls would have been desirable. Due to many attending centers, information collection was not complete, which has an impact especially on the quality of life analysis. A structured quality of life form would have been advantageous for the data collection. Whether patients did go to school or daycare was to a great extent influenced by the opinions of the parents. The time until requirement of strong opioids was influenced by local customs and wishes of the parents. Since the radiological findings are difficult to interpret and do not always correlate with the clinical state of the patient [7], quality of life analysis might be an important measurable parameter in forthcoming studies.

We conclude that the triple anti-angiogenic medication with thalidomide, etoposide, and celecoxib was generally well tolerated with acceptable adverse effects and allowed a good quality of life. The patients were ambulatory and at home. There was a subgroup of patients with DIPG who particularly benefited from this program and survived between 24 and 60 months from diagnosis. More studies with larger patient materials are needed, in addition to a more thorough analysis of the molecular characteristics of tumor biopsies for more targeted therapy in the future.

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