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Original Article

Bevacizumab-containing regimens for children with relapsed or refractory tumors

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Abstract

Background: We aimed to evaluate the effect of bevacizumab-containing regimens (BCRs) on the survival of children with relapsed or refractory solid tumors.

Materials and Methods: Files of children with relapsed or refractory solid tumors treated with BCR were retrospectively reviewed for age, gender, follow-up time, histopathological diagnosis, adverse events observed with BCR, number of chemotherapy protocols used before BCR, the best overall response obtained with BCR, time to progression, number of BCR courses given to patients, the status of patient at last visit, and outcome.

Results: Thirty patients (16 boys, 14 girls) were treated with BCR. The median age at diagnosis was 8.5 (2 - 17) years and at the time of the study was 11 (3-21) years. The median follow-up time was 25.7 (5-79.4) months. The median follow-up time after the start of BCR was 3.2 (1-27) months. Histopathological diagnosis was central nervous system tumors in 25, Ewing sarcoma in two, osteosarcoma in two, and rhabdomyosarcoma in one patient. BCR was given as second-line in 21, third-line in six, and fourth-line protocol in three patients. No chemotherapy toxicity was observed in 22 (73.3%) patients. The best overall response was progressive disease in 17 (56.7%), partial response in seven (23.3%), and stable disease in 6 (20%) patients at first-response evaluation. The median time until progression was 77 (12-690) days. During the study period, 17 patients died of progressive disease.

Conclusion: Our study revealed that adding antiangiogenic agent bevacizumab to cytotoxic chemotherapy provided no survival benefit in children with relapsed or refractory solid tumors.

Keywords:
Bevacizumab, children, refractory, relapse, solid tumors

Introduction

After anti-CD20 monoclonal antibody rituximab had been introduced to clinical use in 1997, numerous new targeted therapy agents have been identified especially in the field of medical oncology. However, these advances in the treatment of adult patients with cancer have not been observed in pediatric oncology. In 2009, U.S. Food and Drug Administration (FDA) approved bevacizumab usage in recurrent glioblastoma multiforme (GBM) in adults.[1]

Bevacizumab, the first used antivascular endothelial growth factor (anti-VEGF) monoclonal antibody in cancer, was combined with other chemotherapeutic

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Website: www.indianjcancer.com	Quick Response Code:
DOI: 10.4103/ijc.IJC_907_20	

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How to cite this article: Yağcı-Küpeli B, Pehlivan D. Bevacizumab-containing regimens for children with relapsed or refractory tumors. Indian J Cancer 0;0:0.

Submitted: 11-Aug-2020 **Revised:** 11-Feb-2021
Accepted: 07-Mar-2021 **Published:** 29-Jun-2022

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agents in many cancers except for GBM indication where it is used as a single agent following radiotherapy.[2]

Knowledge about the efficacy of bevacizumab-containing regimens (BCRs) in pediatric cancer comes from anecdotal case reports, retrospective case series, and Phase I and Phase II studies.[3-9] Although targeting angiogenesis in highly proliferative pediatric cancers seems logical, the exact role of antiangiogenic treatment has not been proven. No survival benefit has been shown with the usage of bevacizumab in the treatment of relapsed or refractory solid tumors in children.[3,4,6,7] Similar discouraging results have been reported in a newly published study evaluating the efficacy of the addition of bevacizumab to multiagent chemotherapy in the treatment of metastatic nonrhabdomyosarcoma soft tissue sarcomas.[7]

Treatment of relapsed or refractory tumors in children remains a challenge in many aspects. First, cumulative doses of effective chemotherapeutics reach critical thresholds with first-line protocols. Second, resistance to used chemotherapy agents occurs before findings of relapse become apparent. Third, some certain permanent side effects of drugs emerge in most of the patients causing difficulties in maintaining chemotherapy. Four, finding effective protocols or drugs in relapsed or refractory pediatric cancers is extremely difficult because of lacking clinical trials. Therefore, pediatric oncologists are helplessly seeking results of retrospective pediatric series or sometimes follow the adult guidelines in designating treatment of relapsed or refractory tumors. To make such an effort, we decided to use bevacizumab, irinotecan, and temozolomide ± vincristine protocol in relapsed or refractory solid tumors of children. However, bevacizumab is not approved for use in children in Turkey. After off-label use approval was obtained by individual application to medical drug and device institution, 30 patients were treated with BCR. Herein we aimed to find out the contribution of antiangiogenic BCR on the survival of children with relapsed or refractory solid tumors.

Materials and Methods

Files of children with relapsed or refractory solid tumors who were treated with BCRs between January 2013 and January 2019 were retrospectively reviewed after institutional review board approval (approval number: 166, 28.02.18) was obtained. Age, gender, follow-up time, histopathological diagnosis, time of BCR start, adverse events observed with BCR, number of chemotherapy protocols used before BCR, the best overall response obtained with BCR, time to progression after BCR, number of BCR courses given to the patients, the status of the patient at last visit and outcomes were recorded. Chemotherapy toxicity was evaluated and recorded according to Common Terminology Criteria for Adverse Events Version 5.0.[10] Response evaluation was made according to the Response Evaluation Criteria in Solid Tumors guidelines.[11] Partial response (PR) was defined as a 30% decrease in the longest diameter of the mass. Progressive disease (PD) was defined as a 20% increase in the longest dimension of the mass. Stable disease was used for patients in whom neither PR nor PD criteria were detected. Patients without additional symptoms or clinical deterioration were evaluated with magnetic resonance imaging (MRI) or positron-emission tomography–computerized tomography (PET-CT) after three courses of BCR (first-response evaluation). Patients who experienced new symptoms or clinical findings after the start of BCR were accepted as clinical progression and evaluated immediately. In case of clinical or radiological progression, BCR was stopped. Follow-up time, time to progression, and follow-up time after BCR were calculated.

Statistical Package for the Social Sciences (SPSS) Version 24.0 was used for data analysis. Descriptive analyses were used for demographic and clinical variables.

Results

There were 30 patients (16 boys, 14 girls). The median age at diagnosis was 8.5 (2-17) years and median age at the time of the study was 11 (3-21) years. The median follow-up time was 25.7 (5-79.4) months. The median follow-up time after the start of the BCR was 3.2 (1-27) months. Cancer types were CNS (central nervous system) tumors in 25 patients (14 medulloblastomas, three anaplastic ependymomas, three diffuse intrinsic pontine gliomas, three glioblastomas, one pineoblastoma, one atypical teratoid rhabdoid tumor), Ewing sarcoma in two patients, osteosarcoma in two patients, and rhabdomyosarcoma in one patient. Bevacizumab was given at a dose of 10 mg/kg every 15 days in combination with irinotecan (150 mg/m^2 in every 15 days) and temozolomide (150 mg/m^2 in every 28 days) in 25 patients and 15 mg/kg in five patients in combination with vincristine (1.5 mg/m^2), irinotecan (150 mg/m^2), and temozolomide (150 mg/m^2 in every 21 days). BCR was given as second-line protocol in 21 patients, third-line protocol in six patients, and fourth-line protocol in three patients. The median BCR course

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Key Message

Bevacizumab-containing regimens provide no survival benefit in children with relapsed or refractory tumors.

number was 3 (range: 1–18 courses). No significant side effect was observed in 22 patients. Grade 1 neutropenia was observed in three patients, Grade 1 thrombocytopenia was observed in three patients, Grade 1 anemia was observed in one patient, and Grade 3 hyponatremia was observed in one patient.

Progressive disease was detected in 17 (56.7%) patients, partial response in seven (23.3%) patients, and stable disease in 6 (20%) patients at first-response evaluation. Extent/stage of the disease, prior treatment modalities, prior chemotherapy courses, duration form diagnosis to beginning of BCR (months) response to BCR at first evaluation, time to progression after BCR, and outcomes according to tumor types are presented in Table 1. The most durable responses were observed in three patients with stable clinical and radiological findings. Twenty-seven patients subsequently developed progressive disease. The median time to progression was 77 (12-690) days. Among patients with a longer duration of stable disease, one with Ewing sarcoma sustained with stable pelvic mass [Figure 1a and b] for 23 months despite irregular attending to chemotherapy because of social issues (18 courses of chemotherapy were given in 23 months). This patient's mass was inoperable, and BCR was started after radiotherapy. The second patient had medulloblastoma and remained with a stable disease for 15.6 months. The third patient had a pontine high-grade glioma and remained with stable pontine mass for 11.2 months. During the study period, 17 patients died of progressive disease. At the end of the study period, 13 patients were alive with some degree of disease and continued BCR or other regimens started after BCR.

Discussion

Vascular endothelial growth factor and its receptors have been used as targets for nearly 20 years in terms of antiangiogenic treatment strategies. Objective responses were obtained with bevacizumab in renal cell carcinoma, glioblastoma, and colorectal cancers in adults.[12-14] Only progression-free survival advantage with the addition of bevacizumab to standard chemotherapy protocol has been shown in adults with some types of advanced-stage cancers.[15] After the studies with breast cancer and colorectal cancer in adults failed to reveal survival advantage with adjuvant usage of bevacizumab, suspicions have arisen about using bevacizumab in treating pediatric cancers.[16] We investigated the role of BCR in a small number of patients with relapsed or refractory solid tumors in our study.

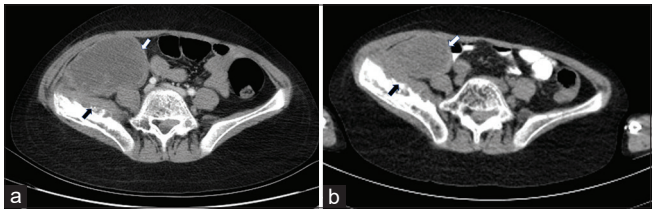

Figure 1: (a and b) Pelvic computerized tomography revealing pelvic mass with illiac bone destruction at the beginning (a) and 23rd month (b) of BCR treatment

The best overall responses observed in our study were progressive disease in 17, partial response in seven, and stable disease in six patients on first-response evaluation. Interestingly, the most durable responses were observed in three patients in whom the stable disease was seen at first-response evaluation. However, the median time to progression was shorter than 3 months in the whole study group. BCR was well tolerated in our patients, and Grade I neutropenia, thrombocytopenia, and anemia were the most common chemotherapy-related toxicities.

In 2008, Glade Bender *et al*. performed a Phase I study in pediatric refractory solid tumors in which usage of bevacizumab at doses of 5, 10, and 15 mg/kg every 2 weeks in 28 days was well tolerated and no dose-limiting toxicity was observed.[17] In 2009, some degree of objective responses was reported with bevacizumab and irinotecan protocol in 7 of 10 pediatric multiply recurrent low-grade gliomas.[17] In 2013, Aguilera *et al.* reported nine relapsed medulloblastoma patients treated with bevacizumab, irinotecan ± temozolomide.[3] The median time to progression was reported as 11 months, and median overall survival was reported as 13 months in this study. At the third month of treatment, partial response was obtained in six of the nine patients. In 2017, the same chemotherapy protocol was used in relapsed neuroblastoma patients in Phase II study setting, and no response or progression was observed in 30 of 33 patients.[4] Another Phase II study evaluating the efficacy of adding bevacizumab versus temsirolimus to cytotoxic chemotherapy in children with rhabdomyosarcoma at first relapse showed event-free survival advantage in the temsirolimus group.[18]

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Table 1: Extent/stage of the disease, prior treatment modalities, prior chemotherapy courses, response to BCR at first evaluation, time to progression after BCR, and outcomes according to tumor types

Patient number	Diagnosis	Extent of the disease/ Stage*	Prior treatment modalities	Prior chemotherapy courses	Duration from diagnosis to beginning of BCR (months)	Response to BCR at first evaluation	Time to progression after BCR (days)	Outcome (at the end of study period)
1	Medulloblastom	Posterior fossa mass without metastasis/ T3aM0	Surgery Radiotherapy Chemotherapy	3 courses of vincristine, etoposide, carboplatin/ cyclophosphamide	5	Stable disease	469	Under treatment
2	Medulloblastoma	4th ventricular mass with spinal seeding at C3-T6 / T3aM3	Surgery Radiotherapy Chemotherapy	12 courses of vincristine, etoposide, carboplatin/ cyclophosphamide	21	Stable disease	266	Died of disease
3	Medulloblastoma	4th ventricular mass with infundibular nodular metastasis/ T3bM2	Surgery Radiotherapy Chemotherapy	14 courses of courses of vincristine, etoposide, carboplatin/ cyclophosphamide	15	Partial response	252	Died of disease
4	Medulloblastoma	Vermian mass without metastasis/ T3aM0	Surgery Radiotherapy Chemotherapy	10 courses of vincristine, etoposide, carboplatin/ cyclophosphamide	22	Stable disease	179	Under treatment
5	Medulloblastoma	4th ventricular mass without metastasis/ T4M0	Surgery Radiotherapy Chemotherapy	14 courses of courses of vincristine, etoposide, carboplatin/ cyclophosphamide	14	Progressive disease	114	Died of disease
6	Medulloblastoma	Cerebellar mass with nodular metastatic lesions near medulla oblongata and C2 level/ T3bM3	Surgery Radiotherapy Chemotherapy	10 courses of vincristine, etoposide, carboplatin/ cyclophosphamide	12	Progressive disease	98	Died of disease
7	Medulloblastoma	Posterior fossa mass without metastasis/ T3aM0	Surgery Radiotherapy Chemotherapy	6 courses of vincristine, lomustine, cisplatin/ cyclophosphamide	31	Partial response	80	Died of disease
8	Medulloblastoma	Posterior fossa mass without metastasis/ T3aM0	Surgery Radiotherapy Chemotherapy	10 courses of vincristine, etoposide, carboplatin/ cyclophosphamide	14	Progressive disease	77	Under treatment
9	Medulloblastoma	Posterior fossa mass without metastasis/ T3aM0	Surgery Radiotherapy Chemotherapy Gamma-knife treatment	12 courses of vincristine, etoposide, carboplatin/ cyclophosphamide	49	Progressive disease	48	Died of disease
10	Medulloblastoma	Posterior fossa mass without metastasis/ T4M0	Surgery Radiotherapy Chemotherapy	7 courses of vincristine, etoposide, carboplatin/ cyclophosphamide 2 courses of nimotuzumab+vinorelbine	12	Progressive disease	34	Died of disease

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Table 1: Contd...

Patient No.	Diagnosis	Extent of the disease/ Stage*	Prior treatment modalities	Prior chemotherapy courses	Duration from diagnosis to beginning of BCR (months)	Response to BCR at first evaluation	Time to progression after BCR (days)	Outcome (at the end of study period)
11	Medulloblastoma	Posterior fossa mass with cerebellar nodular metastases/ T4M2	Surgery Radiotherapy Chemotherapy	12 courses of vincristine, etoposide, carboplatin/ cyclophosphamide	13	Progressive disease	12	Died of disease
12	Medulloblastoma	4th ventricular mass without metastasis/ T2M0	Surgery Radiotherapy Chemotherapy	10 courses of vincristine, etoposide, carboplatin/ cyclophosphamide	39	Partial response	-	Under treatment
13	Medulloblastoma	4th ventricular mass with diffuse spinal metastasis/ T4M3	Surgery Radiotherapy Chemotherapy	14 courses of vincristine, etoposide, carboplatin/ cyclophosphamide	16	Partial response	-	Under treatment
14	Medulloblastoma	4th ventricular mass with diffuse spinal metastasis/ T4M3	Surgery Radiotherapy Chemotherapy	14 courses of vincristine, etoposide, carboplatin/ cyclophosphamide	20	Partial response	-	Under treatment
15	Anaplastic ependymoma	4th ventricular mass without metastasis	Surgery Radiotherapy Chemotherapy	10 courses of vincristine, etoposide, carboplatin/ cyclophosphamide	15	Progressive disease	90	Died of disease
16	Anaplastic ependymoma	4th ventricular mass without metastasis	Surgery Radiotherapy Chemotherapy	10 courses of vincristine, etoposide, carboplatin/ cyclophosphamide	28	Progressive disease	64	Died of disease
17	Anaplastic ependymoma	4th ventricular mass without metastasis	Surgery Chemotherapy Radiotherapy Gamma-knife treatment	6 courses of ifosfamide, carboplatin, and etoposide	65	Stable disease	–	Under treatment
18	Diffuse intrinsic pontine glioma	Pontine mass	Surgery Radiotherapy Chemotherapy	Radiotherapy and concomitant temozolomide 4 courses of nimotuzumab, vinorelbin	6	Partial response	336	Under treatment
19	Diffuse intrinsic pontine glioma	Pontine mass	Surgery Radiotherapy Chemotherapy	Concomitant temozolomide with radiotherapy 8 courses of temozolmide	11	Progressive disease	12	Died of disease
20	Astroblastoma	Right frontotemporal mass without metastasis	Surgery Radiotherapy Chemotherapy	12 courses of vincristine, etoposide, carboplatin/ cyclophosphamide	30	Progressive disease	51	Died of disease

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Table 1: Contd...

Patient No.	Diagnosis	Extent of the disease/ Stage*	Prior treatment modalities	Prior chemotherapy courses	Duration from diagnosis to beginning of BCR (months)	Response to BCR at first evaluation	Time to progression after BCR (days)	Outcome (at the end of study period)
21	Glioblastoma multiforme	Left parietal mass without metastasis	Surgery Radiotherapy Chemotherapy	Concomitant temozolomide with radiotherapy 4 courses of temozolomide, 10 courses of vincristine, etoposide, carboplatin/ cyclophosphamide	19	Progressive disease	146	Died of disease
22	Glioblastoma multiforme	Left cerebellar mass extending to brainstem	Surgery Radiotherapy Chemotherapy	Concomitant temozolomide with radiotherapy 2 courses of temozolomide	4	Partial response	–	Under treatment
23	Glioblastoma multiforme	Frontotemporal mass without metastasis	Surgery Radiotherapy Chemotherapy	6 courses of vincristine, etoposide, carboplatin/ cyclophosphamide 3 courses of ifosfamide, carboplatin, etoposide	24	Progressive disease	37	Died of disease
24	Pineoblastoma	3rd ventricular mass without metastasis	Surgery Radiotherapy Chemotherapy	1 course of vincristine, carboplatin, etoposide 9 courses of cisplatin, etoposide	10	Stable disease	–	Under treatment
25	Atypical teratoid rhabdoid tumor	Posterior fossa mass with multiple cerebral nodular metastases	Surgery Radiotherapy Chemotherapy	10 courses of vincristine, etoposide, carboplatin/ cyclophosphamide,	22	Progressive disease	100	Under treatment
26	Osteosarcoma	Right distal femoral mass without distant metastasis/ T2N0M0	Surgery Chemotherapy	40-week chemotherapy with cisplatin, adriamycin, methotrexate, ifosfamide, etoposide 6 courses ifosfamide, carboplatin, topotecan 3 courses of vincristine, irinotecan, temozolomide 4 courses of sirolimus, zoledronic acid	39	Progressive disease	220	Under treatment
27	Osteosarcoma	Left femoral mass with vertebral metastasis at L1 level/ T2N0M1	Surgery Chemotherapy	24-week chemotherapy with cisplatin, adriamycin, methotrexate, ifosfamide, etoposide 6 courses of ifosfamide, carboplatin, etoposide 3 courses of vincristine, irinotecan, temozolomide	16	Progressive disease	70	Died of disease

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Table 1: Contd...

Patient No.	Diagnosis	Extent of the disease/ Stage*	Prior treatment modalities	Prior chemotherapy courses	Duration from diagnosis to beginning of BCR (months)	Response to BCR at first evaluation	Time to progression after BCR (days)	Outcome (at the end of study period)
28	Ewing's sarcoma	Left humerus mass with left axillary metastatic lymph node/ T2N1M0	Surgery Chemotherapy Radiotherapy	6 courses of vincristine, ifosfamide, doxorubicin, etoposide 4 courses of vincristine, actinomycin D, cyclophosphamide 3 courses of ifosfamide, carboplatin, etoposide 3 courses of vincristine, irinotecan, temozolomide	18	Progressive disease	108	Under treatment
29	Ewing's sarcoma	Pelvic mass with multiple bone and lung metastases/ T2N0M1	Chemotherapy Radiotherapy	4 courses of vincristine, ifosfamide, doxorubicin, etoposide, 6 courses of ifosfamide, carboplatin, topotecan	9	Stable disease	690	Died of disease
30	Rhabdomyosarcoma	Thoracic mass with regional lymph node and pulmonary metastases/ T2N1M1	Surgery Chemotherapy Radiotherapy	5 courses of vincristine, ifosfamide, doxorubicin, etoposide 3 courses of ifosfamide, carboplatin, etoposide, topotecan	7	Progressive disease	27	Died of disease

*Modified Chang's staging in medulloblastoma, TNM (tumor, node, metastasis) staging in osteosarcoma, rhabdomyosarcoma, and Ewing's sarcoma

A few studies are investigating the efficacy of bevacizumab in newly diagnosed pediatric cancers in a prospective setting.[5,7,19] Improvement in overall and event-free survival was not observed in children with high-grade or diffuse intrinsic pontine gliomas treated with valproic acid and bevacizumab treatment in addition to radiotherapy.[5] Similarly, no survival benefit was seen in children with newly diagnosed high-grade glioma treated with bevacizumab in addition to temozolomide and radiation.[19] Ferrari *et al.* reported no survival advantage in patients with metastatic nonrhabdomyosarcoma soft tissue sarcomas treated with chemotherapy and bevacizumab combination compared with patients receiving only chemotherapy.[7] In our study, inoperable pelvic mass remained stable for 23 months in a patient with Ewing sarcoma. BCR was started after radiotherapy in this patient, and this durable response could not be attributed only to the efficacy of antiangiogenic therapy.

In conclusion, the efficacy of bevacizumab in pediatric cancers needs to be further investigated. However, data so far have shown that targeting angiogenesis at only one step by inhibiting VEGF seems to be insufficient in most pediatric cancers. Multiple-step inhibition with combined antiangiogenic molecules may be more effective to prevent metastasis and cure cancer in newly diagnosed, relapsed, or refractory tumors in children.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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