Bevacizumab in Pediatric Patients: How Safe Is It?

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Abstract. Background: Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF). The safety profile of bevacizumab was evaluated in a cohort of children with either recurrent or poor-prognosis malignancies. Patients and Methods: Bevacizumab was administered intravenously at the dosage of 5-10 mg/kg every 14-28 days alone or in combination with other agents. Toxicity was reported according to common toxicity criteria version 4. Results: Seventeen patients received a total of 156 bevacizumab doses (median 5 doses/patient) for a median treatment duration of 2 months (range 1-21). Grade II-III lymphopenia was recorded in 10 patients, while grade III proteinuria and grade I epistaxis occurred in one patient each. Grade III wound dehiscence was observed in one case and 3 severe adverse events (SAEs) were recorded: one reversible posterior leukoencephalopathy syndrome (RPLS) with grade IV seizures and grade IV hypertension, one grade IV hypertension and a post-operative grade IV enterocutaneous fistula. Conclusion: In the present cohort, the overall incidence of SAEs (17%) was higher than previously reported, thus, further studies should be justified to better characterize the safety profile of bevacizumab in the pediatric population.

Angiogenesis is crucial for tumor development, invasion, progression and metastatic spread. It is regulated by the expression of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), initially identified as a tumor-derived factor capable of increasing vascular permeability (1). In the embryo, the role of VEGF in normal vessel development is well known, as it promotes the differentiation, proliferation and survival of endothelial cells and the elaboration of the vascular tree (2). VEGF is expressed in virtually all human tumors. The highest levels of VEGF expression have been associated with increased tumor vascularity, as well as rapid tumor growth, invasion and metastasis. The role of VEGF in tumor growth and angiogenesis was demonstrated by the use of murine monoclonal antibody specific to human VEGF (muMAb VEGF A4.6.1) (3).

VEGF blocking therapy have been demonstrated to have promising anticancer activity both in preclinical studies and early adult Phase I/II trials (4).

Bevacizumab (rhuMab VEGF, Avastin®, Genentech, Inc., South San Francisco, CA, USA) is a humanized monoclonal VEGF-neutralizing antibody, which was approved by the Food and Drug Administration in 2004 for treatment of metastatic colorectal cancer in fluorouracil-containing regimens (5).

The activity of bevacizumab, either alone or in combination with cytotoxic agents, has been demonstrated in adult patients affected by various malignancies (6-10).

The rationale for considering the use of bevacizumab in pediatric cancer patients lies on the observations that serum VEGF levels were found to be elevated in children with several solid tumors and declined to healthy children level after treatment (11) and that this monoclonal anti-VEGF antibody showed inhibition of tumor angiogenesis in preclinical studies on several pediatric tumors, including Wilm’s tumor, neuroblastoma, hepatoblastoma and rhabdomyosarcoma (12-15).

Limited data on the safety and the efficacy of anti-angiogenic agents in paediatric population were available when we started to use bevacizumab in a paediatric population. The main toxicities observed in adult patients treated with bevacizumab included proteinuria, nephrotic syndrome, hypertensive encephalopathy, and headache associated with nausea and vomiting (5).

The toxicity profile of bevacizumab, used either alone or in combination with chemotherapy and other antitumor agents, administered in a compassionate setting to children affected by poor-prognosis tumors, is described.
Patients and Methods

Patients with histologically confirmed either poor-prognosis or resistant/relapsed tumors were eligible for treatment provided they had adequate peripheral blood counts (neutrophils >1,000/mm³ and platelets >75,000/mm³), hepatic (total bilirubinemia <1.5 × upper normal value and aspartate amino transferase /alanine amino transferase <2.5 × upper normal value), and renal (creatininemia <1.5 × upper normal value) function tests. Written informed consent was obtained from either the patient’s parents or their legal guardians. The palliative treatment was approved by the Institutional Review Board.

Between June 2006 and December 2009, 17 patients, 9 males and 8 females, with a median age of 112 months (range 30–222 months), were given bevacizumab at a dosage ranging from 5 to 10 mg/kg intravenously (over a 60–90 minute infusion) every 14 or 28 days. Twelve patients had a relapsed/refractory solid tumor, while five had a poor-prognosis tumor. The diagnoses were neuroblastoma in 7 patients, rhabdomyosarcoma in 4, hepatocellular carcinoma in 3 and renal cell carcinoma, Ewing Sarcoma and abdominal embryonal biphasic tumor in the remaining 3 patients. The clinical features of the patients included in the study are shown in Table I.

Results

A total of 156 doses of bevacizumab were administered, with a median of 5 doses per patient (range 2–25). In 3 patients, bevacizumab was administered as first-line treatment; in one of them a first course of Ifosfamide, Carboplatin and Etoposide was administered for an initial diagnosis of desmoplastic round cell tumor. In the other 14 patients bevacizumab was used as the third or fourth-line therapy following failure of previous treatment. Bevacizumab was used in combination with chemotherapy in 15 patients, together with sunitinib and pegylated–interferon α-2b in one patient and alone in another one. The median treatment duration was 2 months (range 1–21). Nine patients suffered tumor progression during treatment, after a median progression-free interval of 2 months (range 1–13). Three patients stopped bevacizumab in complete remission: two with newly diagnosed hepatocellular carcinoma who were treated for 19 and 21 months, respectively, and one with relapsed rhabdomyosarcoma, who was given the drug for 5 months. One patient refused to continue treatment after one month because of family choice, while four patients discontinued treatment after a median of 5 months (range 1–10) due to the occurrence of grade III-IV toxicity. Table II details treatment with bevacizumab.

Toxicity. Grade II-III lymphopenia was observed in 10 patients, while grade III proteinuria and grade I epistaxis were recorded in one patient each.
A grade III wound dehiscence occurred in a patient with a local relapse of rhabdomyosarcoma of the jaw. In this child, Bevacizumab at the dosage of 10 mg/kg with intravenous vincristine and oral irinotecan, was started 12 days after local surgery with a fully healed wound. Bevacizumab was discontinued soon after the dehiscence occurred.

Three SAEs were observed: case 1, a reversible posterior leukoencephalopathy syndrome (RPLS), case 2, a grade IV entero-cutaneous fistula and case 3 grade IV hypertension.

Case 1 was an eight-year old-boy (patient 4) affected by metastatic neuroblastoma relapsed 8 months from first-line treatment, which was based on conventional and high-dose chemotherapy with autologous peripheral stem cells support, surgery on primary tumor, abdominal radiotherapy and 13-cis-retinoic acid. After failure of third-line chemotherapy based on gefitinib plus oral topotecan and cyclophosphamide, the child received bevacizumab at the dosage of 10 mg/kg every two weeks associated with irinotecan and temozolomide. His blood pressure was normal until 24 h after the fourth dose of bevacizumab when he developed generalized tonic clonic seizures and grade IV hypertension was diagnosed. A second crisis occurred 8 h later. MRI of the brain showed white matter changes consistent with RPLS. He was treated with intravenous diazepam and fenobarbital, while hypertension was controlled by intravenous labetalol. After 10 days, all the neurological symptoms had resolved and blood pressure was normal on anti-hypertensive treatment. A new MRI showed regression of RPLS. He was discharged on oral fenobarbital, labetalol and ramipril which were reduced 6 months later. Bevacizumab was discontinued.

Case 2 was a fourteen-year-old girl (patient 16) with metastatic renal cell carcinoma, who had experienced relapse after first-line treatment with sorafenib and PEG-IFN α-2b, started bevacizumab at the dosage of 10 mg/kg every two weeks in combination with PEG-IFN α-2b. A CT scan, performed three months later, showed disease progression, so that PEG-IFN α-2b was discontinued and sunitinib (25 mg daily orally for 4 weeks with a two-week rest period) in combination with bevacizumab at the dosage of 10 mg/kg every 2 weeks was administered. After two months of treatment, a CT scan showed a partial remission of disease. After six months and 21 doses of bevacizumab, the girl presented grade IV hypertension and grade III proteinuria. Treatment with sunitinib and bevacizumab was discontinued and anti-hypertensive therapy with amlodipina besilate, carvedilol and ramipril was started, achieving blood pressure control. Sunitinib was re-started, while
bevacizumab was discontinued. Asymptomatic hypothyroidism requiring substitutive treatment with levotiroxine and nephrotic syndrome were diagnosed 1 month and 5 months after bevacizumab discontinuation, respectively.

Case 3 was a thirty-two-month-old boy (patient 17) with an abdominal biphasic embryonal tumor, relapsed after multimodal treatment (surgery, conventional and high-dose chemotherapy, intra-peritoneal chemotherapy). Bevacizumab was started 17 days after surgery. After the second administration, the child underwent abdominal surgery with complete removal of a local relapse. Twenty days later, he restarted treatment with bevacizumab and received 5 further doses. Two weeks after the seventh administration, a grade IV enterocutaneous fistula developed. The patient needed a 20-cm colic resection; bevacizumab was discontinued.

Discussion

Although clinical experience in pediatric patients is still limited, from available data, bevacizumab seems to be safe in children, with well manageable adverse effects.

In the Children Oncology Group phase I trial, the bevacizumab dosage was increased up to 15 mg/kg from 5 mg/kg with no dose-limiting toxicity and only one grade III bevacizumab-related lymphopenia (17). In the experience of benesch M and colleagues bevacizumab at a dosage of 5-10 mg/kg intravenously every 2-3 weeks was well tolerated, even in four patients treated for more than 10 months. Two patients developed hypertension not requiring treatment, while nose bleeding and proteinuria were observed in two patients and local erythema and defective wound healing in one (18).

In two recent paper, bevacizumab presented a good safety profile in primary central nervous system (CNS) tumor used alone or in combination with other cytotoxic drug (19, 20). A grade III hypertension, grade III proteinuria and grade III hypertension in combination with nephrotic syndrome were recorded in one patient (19) and a grade IV CNS ischemia in two patients when used with irinotecan (20).

In terms of side effects related to the use of bevacizumab, hypertension seems to be the most frequent one. In a meta analysis, the frequency of bevacizumab-associated hypertension was 16%, considering seven prospective and randomized controlled trials on adults, and there was no relationship between bevacizumab dosage or treatment duration and hypertension (21). Thus, the authors suggested routine measurement of blood pressure during and after bevacizumab treatment for four to six months (21).

In the present study, grade IV hypertension was recorded in 2/17 (12%) patients; this incidence was remarkable considering the young age and the absence of additional risk factors (smoking, diabetes, hypercholesterolemia etc.) in the studied population. Both instance of grade IV hypertension occurred in patients previously treated with tyrosine kinase inhibitors. Thus the association of bevacizumab with tyrosine kinase inhibitors may have increased the risk of hypertension. One of these two patients also developed a RPLS.

RPLS is very rare and has been reported in a few adult patients and in one child treated with bevacizumab (22-25). The presenting symptoms are severe headache, nausea, confusion, cortical blindness and seizures, typically associated with acute elevation of blood pressure. At MRI, edema is visible in the white matter of the posterior cerebral hemispheres. Bevacizumab can lead to this adverse event both by increasing the vascular permeability of the blood-brain-barrier and increasing blood pressure (21).

During bevacizumab treatment blood pressure monitoring seems to be mandatory in both adult and pediatric patients and we agree that monitoring should be continued for a few months after bevacizumab discontinuation.

In the present series, a bowel perforation with enterocutaneous fistula formation occurred in a child with a relapsed abdominal tumor. The reported overall frequency of bowel perforation in patients treated with bevacizumab is about 1.5%. Risk factors include an endoscopy within one month, abdominal radiotherapy, the use of non-steroidal anti-inflammatory drugs for one month or more, peptic ulcer disease, diverticulitis, chemotherapy-induced colitis and previous surgery and the BC Cancer Agency suggests discontinuation of bevacizumab at least six to eight weeks before elective bowel surgery (26). In the present case, the enterocutaneous fistula was far from the surgical site, but probably the multiple abdominal surgery procedures performed and the early use of bevacizumab played a role.

Angiogenesis is involved in wound healing, so during bevacizumab therapy impaired wound healing could occur (27) and a delay of at least 4 weeks after surgery or until the wound is fully healed is recommended before starting bevacizumab (26). In the present case of grade III wound dehiscence, the patient had started bevacizumab 21 days after maxillo-facial surgery with a fully healed wound.

All the present instance of grade II-III lymphopenia occurred in patients receiving concomitant cytotoxic drugs so that was difficult to identify bevacizumab-related lymphopenia.

However all the present patients, but one, received bevacizumab in combination with other antiblastic treatment, thus the efficacy of bevacizumab could not be evaluated. Nevertheless, 3 patients, treated for 5, 19 and 21 months, were alive in complete remission at 43, 35 and 34 months from the start of bevacizumab.

In summary, the present incidence of grade III-IV toxicity seems to be higher than reported in other pediatric series (17-20). Probably this difference was due to the characteristics of the present cohort consisting mainly of heavily pre-treated cancer patients. During bevacizumab treatment, careful monitoring of side-effects is mandatory, especially in heavily pre-treated patients and we suggest monitoring for at least 6
months after discontinuing treatment. Monitoring of blood pressure should be more strict in patients previously treated with tyrosine kinase inhibitors and Bevacizumab treatment should be withheld for at least 4 weeks from major surgery and, whenever indicated, careful wound evaluation should be performed.

Further studies with a large cohort are needed to clarify the safety profile and to assess the clinical benefit of bevacizumab in pediatric cancer patients.

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References

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