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Bevacizumab and PEGylated Liposomal Doxorubicin in the Treatment of Relapsed Osteosarcoma

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Abstract

Background: Treatment of relapsed osteosarcoma is challenging and prognosis is dismal. Many second-line treatments have been tried with no breakthrough in response rate. PEGylated liposomal doxorubicin and bevacizumab have been shown to be effective in treating sarcomas, but they were never given in combination for osteosarcoma patients.

Methods: A restrospective case review of 3 patients with relapsed or refractory osteosarcoma who were treated with bevacizumab (5 to 15 mg/kg every 2 to 8 weeks) and PEGylated liposomal doxorubicin (50 mg/m2 every 3 to 4 weeks) was undertaken.

Results: Two of three patients received a complete remission on this treatment with event-free survival of 7.6 years and 4.3 years on their last follow-up. Toxicity profile was acceptable for bevacizumab with 1of 3 patients experiencing mild proteinuria which resolved with dose reduction. 1 of 3 patients suffered a severe side effect of PEGylated liposomal doxorubicin (palmoplantar erythrodysesthesia) that forced us to withhold the treatment.

Conclusion: A combination of bevacizumab and PEGylated liposomal doxorubicin could be an efficient treatment option for patients with relapsed osteosarcoma suffering minimal disease.

Introduction

Osteosarcoma is the most common primary bone tumor in children and adolescents [1]. Before chemotherapy, surgical resection of the primary tumor was the only treatment modality available. Despite achieving complete resection of the primary tumor, 80% of patients suffered disease recurrence [2]. With the introduction of adjuvant chemotherapy in the early 1970's event-free survival percentage has increased by 4 folds [2]. Later in the 1970's, Rosen and Marcove developed the concept of using chemotherapy prior to performing an En-bloc resection of the primary tumor (neoadjuvant chemotherapy) [3]. They demonstrated an advantage of this modality and found a correlation between histological response and subsequent disease-free survival. However, no major progress has been achieved during the past decade. Even with the use of the most active chemotherapy (Methotrexate, Doxorubicin, and Cisplatin) the 5-year survival rate for non-metastatic osteosarcoma is still between 60% to 70% [4-6]. The outcome for patients with macroscopic metastatic disease upon diagnosis remains much worse with 2-years-survival of less than 30% [7]. Patients who respond poorly to frontline chemotherapy and develop refractory or recurrent disease also have dismal prognosis. Several second-line chemotherapy regimens have been tried in an attempt to improve outcome, but they proved to be of minimal benefit at best [8].

Angiogenesis is a crucial process in tumor growth and Vascular Endothelial Growth Factor (VEGF) is one of the main mediators of this process [9]. By binding to its receptor, VEGF activates a myriad of signaling pathways promoting endothelial cell proliferation, migration, and survival [9]. Furthermore, VEGF induces vascular hyperpermeability which may lead to malignant effusions [10]. Interestingly, angiogenesis was found to be predictive of metastasis and poor prognosis in osteosarcoma [11]. Due to this fundamental role in tumorigenicity, VEGF serves as a potential target for cancer treatment, including osteosarcoma.

Bevacizumab (Avastin) is a humanized, monoclonal anti-VEGF antibody, consisting of about 93% human and 7% murine protein sequence. It is capable of neutralizing all isoforms of human VEGF [12]. Several randomized controlled trials have evaluated the benefit of adding Bevacizumab to standard chemotherapy regimens for patients with metastatic solid tumors. A meta-analysis of 24 of these studies concluded that the addition of bevacizumab to chemotherapy in patients with metastatic solid tumors resulted in a statistically significant improvement of overall survival and

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Table I: Summary of Patient Characteristics and Treatment.

	Patient 1	Patient 2	Patient 3
Age at 1st diagnosis (years)	12.5	18	8
Gender	F	M	M
Treatment received prior to bevacizumab and PLD	MAP, surgery, INF-α, IE, Radiotherapy, Ridaforolimus, Gemcitabine+Docetaxel	MAP/MAPIE, surgery, ifosfamide, radiotherapy, mifamurtide	MAP, mifamurtide, IE, surgery
Disease status upon treatment initiation	Microscopic disease	Microscopic residual disease	Miliary spread of pulmonary metastases
Pegylated Liposomal Doxorubicin			
Dose (mg/m^2)	40	40	40
Frequency of administration	Every 4 weeks	Every 4 weeks	Every 3 weeks
Number of treatment cycles	6	12	4
Cumulative dose received (mg/m^2)	240	480	160
Bevacizumab			
Dose (mg/kg)	5	5	10-15
Frequency of administration	Every 2-8 weeks	Every 2-8 weeks	Every 2 weeks
Total number of treatment cycles	84	53	10
Response	Complete Remission	Complete Remission	Progressive Disease
Side effects attributed to Bevacizumab	Mild Proteinuria	None	None
Side effects attributed to PLD	None	None	Severe Palmoplantar Erythrodysesthesia

Abbreviations: MAP: Doxorubicin (37.5 mg/m^2/day), Adriamycin (60 mg/m^2/day), Methotrexate (12 g/m^2/day); MAPIE: Doxorubicin (37.5 mg/m^2/day), Adriamycin (60 mg/m^2/day), Methotrexate (12 g/m^2/day), Ifosfamide (1.8-2.8 g/m^2/day) and etoposide (100 g/m^2/day); IE: Ifosfamide (1.8-2.8 g/m^2/day) and Etoposide (100 g/m^2/day); PLD: Pegylated Liposomal Doxorubicin

progression-free survival [13]. However, clinical application did not prove as effective as the experiments for osteosarcoma. A phase II trial evaluating the effect of adding Bevacizumab to standard frontline osteosarcoma treatment (Methotrexate, Doxorubicin and Cisplatin) concluded that this combination did not appear to improve histologic response or outcome for patients with localized osteosarcoma [14].

Many of the protocols used for treating osteosarcoma are still based on Doxorubicin along with Methotrexate and Cisplatin, and sometimes Ifosfamide, Etoposide, or other drugs [15]. A major limitation for the use of Doxorubicin is its cardiotoxicity that is related to the cumulative dose, and CHF incidence is reported to be as high as 48% in patients who had receive a cumulative dose of 700 mg/m^2 [16]. Therefore, the total cumulative dose of Doxorubicinis usually limited to 400 to 450 mg/m^2 in practice, rendering this drug hard to use in recurrent disease. PEGylated liposomal doxorubicin is a liposomal formulation of doxorubicin. Its long circulation time with stable retention of the payload and its accumulation in tumors with high vascular permeability result in important advantages over conventional doxorubicin [17]. In addition, Cumulative doses of more than 500 mg/m^2 of PEGylated liposomal doxorubicin were shown to have a considerably lower risk of cardiomyopathy than conventional doxorubicin [18]. A significant antitumor activity of PEGylated liposomal doxorubicin has been reported in a number of cancers, including soft tissue sarcomas [17].

In this article, we report 3 cases of relapsed osteosarcoma treated with a novel combination of bevacizumab and PEGylated liposomal doxorubicin.

Case 1

(See timeline 1 for summary)

A 12.5 years old girl presented with pain and swelling of her right knee. Radiologic evaluation including plain X-ray and Magnetic Resonance Imaging raised suspicion for osteosarcoma. Pathologic examination taken from an open biopsy confirmed the diagnosis. Screening tests prior to treatment were normal. Treatment was initiated with Adriamycin (37.5 mg/m^2/day with addition of Dexrazoxane as cardio-protection), Cisplatin (60 mg/m^2/day), and Methotrexate (12 g/m^2/day). She underwent surgery in which a tumor of 8.5 cm × 4 cm diameter was totally resected, including the right distal femur and the growth plate. Pathologic examination demonstrated free margins and 99% tumor tissue necrosis. After recovering from surgery her chemotherapeutic regimen was resumed (Over a duration of 40 weeks she received a total of 4 doses of Adriamycin, 4 doses of Cisplatin, and 14 doses of Methotrexate,) and a complete remission was achieved before the end of the regimen. Follow-up Computed Tomography scan performed 1.5 years after her initial diagnosis demonstrated a solitary pulmonary nodule of 1.2 cm diameter in the right upper lobe. A complete surgical resection was performed and pathologic examination confirmed it was osteosarcoma metastasis. Soon after recovery we started treatment with PEGylated interferon-α (1 μg/kg weekly). She had received it for 3 months until a follow-up CT scan demonstrated disease progression with 3 pulmonary metastases (3 cm × 4.5 cm and 1 cm × 1 cm in Left Upper Lobe, 1 cm × 2 cm in the left pleura). Interferon-α was stopped and replaced by ifosfamide (1.8 g/m^2/day) and Etoposide (100 mg/m^2/day). After having completed two cycles, CT scan demonstrated resolution of 2 nodules and persistence of one (3.2 cm × 3.1 cm in LUL). This nodule was removed surgically by wedge resection. Pathologic examination of the resected tissue demonstrated an osteosarcoma metastasis with 90% necrosis. After recovering from surgery, she received a third course of ifosfamide & etoposide. This course was complicated by Fanconi syndrome for which she received treatment with replacement therapy and a long follow-up in the nephrology clinic. One month later, she started receiving radiation therapy with a total of 40 Gy in 20 fractions. She developed grade-I radiation esophagitis. Once radiotherapy had been completed we started treatment with ridaforolimus (mTOR inhibitor) based on

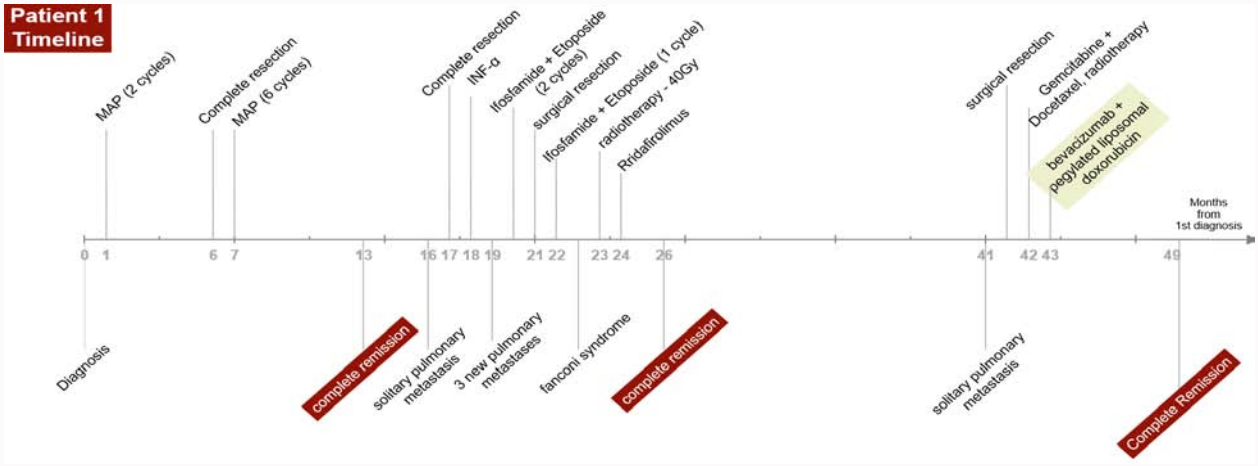

Figure 1: Patient 1 timeline.

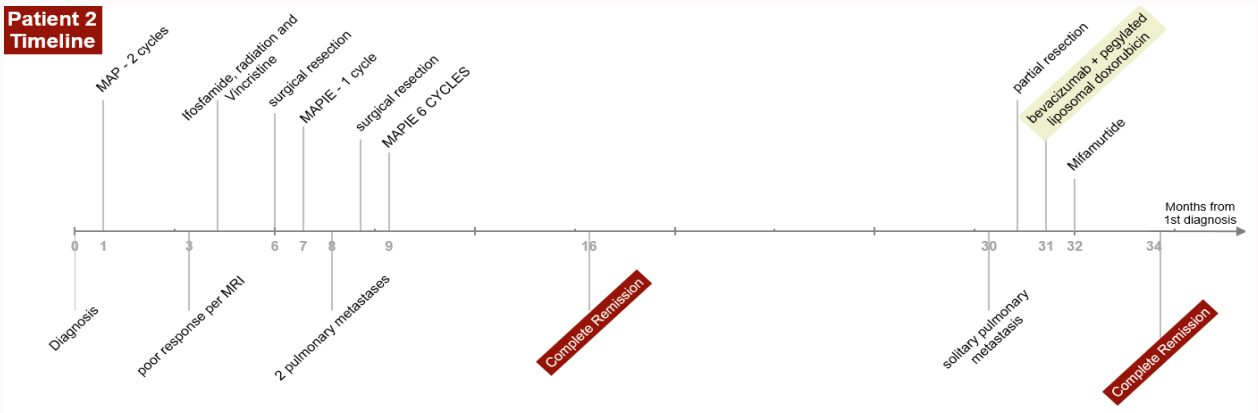

Figure 2: Patient 2 timeline.
MAP: Doxorubicin (37.5 mg/m^2/day), Adriamycin (60 mg/m^2/day), Methotrexate (12 g/m^2/day); MAPIE: Doxorubicin (37.5 mg/m^2/day), Adriamycin (60 mg/m^2/day), Methotrexate (12 g/m^2/day), ifosfamide (1.8-2.8g/m^2/day) and etoposide (100 g/m^2/day)

phase III SUCCEED study [19]. While on this treatment she suffered from enuresis which resolved once the ridaforolimus was stopped. One year later, a benign mass was found and removed from her nasal cavity. Pathologic examination demonstrated fibrous dysplasia with focal chronic inflammation of nasal mucosa. Three months later, an FDG PET-CT scan detected a mass of 2 cm diameter with high FDG uptake in her left posterior chest wall. This mass was removed by wide surgical resection. Pathologic examination demonstrated high-grade osteosarcoma. The tumor tissue was sent for genetic profiling, searching for possible targeted therapy. Once recovered from the surgery, the area of the resected metastasis was radiated (6MV X-ray). Simultaneously she started treatment with docetaxel (75 mg/m^2 every 3 weeks) and gemcitabine (400 mg/m^2 twice monthly) [20]. While on this therapy, genetic profile test showed that microarray assay of TOPO2A implied possible benefit from anthracyclines, and HIF1A overexpression implied possible benefit from Bevacizumab. After several expert consultations and discussions, taking in considerations the mentioned results, we decided to switch to treatment with the combination of PEGylated liposomal doxorubicin (Doxil, 40 mg/m^2 every 3 weeks) and bevacizumab (Avastin, 5 to 10 mg/kg/dose every 2 to 4 weeks). After 2 years on this treatment her creatinine level increased from 1 mg/dL up to 1.3 mg/dL with mild proteinuria and protein/creatinine ratio of 400. Blood pressure and renal US were normal. These findings were attributed to Bevacizumab. We reduced the infusion frequency to once a month (instead of once every 2 weeks) and her creatinine and urinary protein decreased to normal range. Bevacizumab was given in 84 cycles over a period of 7.3 years, during which complete remission was maintained. On her last follow-up, she was still in complete remission 7.6 years from her last relapse.

Case 2

(See patient 2 timeline for summary)

An 18-years-old male patient was referred to our medical center with a diagnosis of chondroblastic osteosarcoma involving the left sacrum and ileum. Diagnosis was based on pathologic examination of tissue biopsy performed on another medical center. Echocardiography, pulmonary function tests, chest X-ray, audiogram, and complete blood count were within normal range at diagnosis. Blood chemistry revealed markedly elevated alkaline phosphatase level (2441 U/L). LDH level was borderline. After completing all screening tests, chemotherapy regimen (AOST-0331 protocol) consisting of Doxorubicin (37.5 mg/m^2/day), Cisplatin (60 mg/m^2/day), and Methotrexate (12 g/m^2/day) was initiated. After 10 weeks on chemotherapy his pre-operative evaluation included a Magnetic Resonance Imaging that demonstrated a large unresectable pelvic tumor that increased in size despite chemotherapy. Surgery was postponed and his treatment regimen was intensified with Ifosfamide (3 g/m^2/dose once every 3 weeks), radiation therapy, and

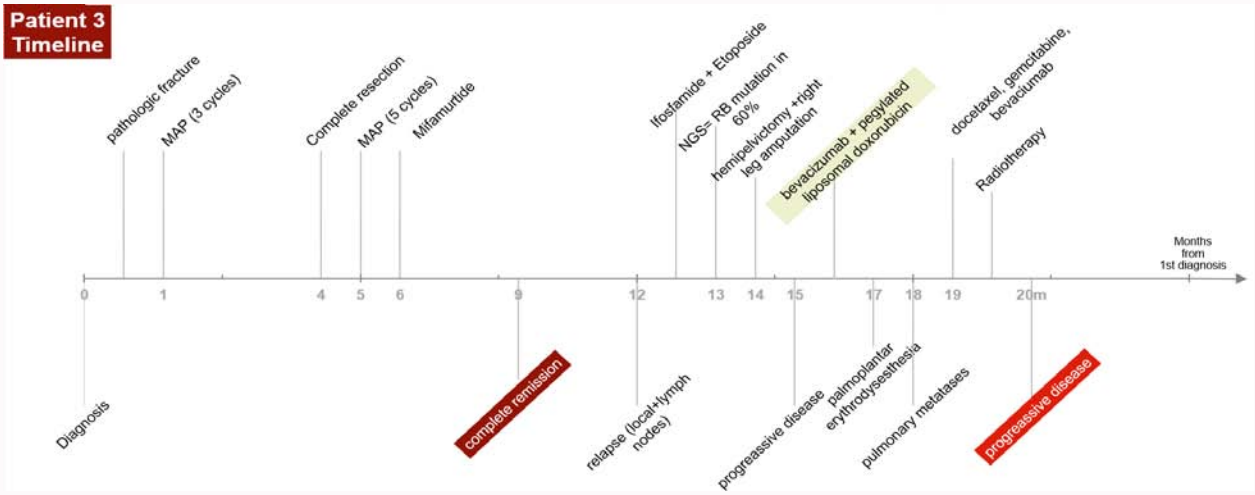

Figure 3: Patient 3 timeline.

Vincristine (maximal dose of 2 mg once a week). Ten weeks later he underwent hemipelvectomy with complete resection of the tumor. Pathologic examination demonstrated 85% necrosis of the tumor tissue. Once recovered from surgery, chemotherapy was resumed by "MAPIE" arm of AOST-0331 protocol (Doxorubicin (37.5 mg/m^2/day), Cisplatin (60 mg/m^2/day), Methotrexate (12 g/m^2/day), ifosfamide (1.8-2.8 g/m^2/day) and etoposide (100 g/m^2/day). One month later CT scan detected two pulmonary nodules in the right lower lobe. Both nodules were resected and pathologic examination confirmed the diagnosis of metastatic osteosarcoma. Upon recovery, chemotherapy regimen was resumed and completed. Complete remission was achieved and our patient was referred to rehabilitation center. 14 months off chemotherapy he suffered another relapse with pulmonary metastasis in right lower lung. The mass was resected and sent to pathologic examination that confirmed the diagnosis of metastatic osteosarcoma, but the resection margins were linked with malignant cells. Three weeks after surgery we started treatment with bevacizumab (5 mg/kg/dose every 2 to 4 weeks), and PEGylated liposomal doxorubicin (60 mg/m^2/dose once a month for 3 cycles). Mifamurtide was added later on (2 mg/m^2 for a total of 48 doses over 36 weeks). Up to the issue date of this article our patient is still in complete remission, 7.3 years from his first diagnosis, 4 years from his last relapse.

Case 3

(See patient 3 timeline for summary)

An 8-years-old boy presented with progressive pain and swelling in his right knee for one month. Plain X-ray revealed a large mass in the right distal femur with the formation of Codman's triangle. Bone scintigraphy showed a remarkable uptake in that area, with no further abnormalities. MRI demonstrated a mass in the distal femur, suspected for osteosarcoma. Chest CT scan revealed no pulmonary nodules. An open biopsy was performed and pathologic examination confirmed the diagnosis of high-grade osteoblastic osteosarcoma. Two weeks later he fell in the bathroom. Radiologic exam revealed a fracture in the right distal femur, adjacent to the biopsy tract. Screening tests, including cardiac echocardiography, pulmonary function tests and audiometry were normal prior to treatment. Chemotherapeutic regimen with Doxorubicin (37.5 mg/m^2/day), Cisplatin (60 mg/m^2/day), and Methotrexate (12 g/m^2/day) was initiated (MAP arm of AOST-0331 protocol). After completing two cycles of chemotherapy, resection of his tumor was postponed due to a delay in having proper prosthesis. Thus he received an additional cycle of chemotherapy followed by surgery in which the tumor was resected altogether with the right distal femur, and X-Pand prosthesis was implanted. Pathologic examination of the tissue demonstrated free margins and 100% necrosis of tumor tissue. Once recovered from surgery he had resumed his chemotherapy regimen. Simultaneously he began treatment with mifamurtide (2 mg/m^2/dose twice a week for 12 weeks and then once a week for 24 weeks). He achieved complete remission by the end of MAP regimen. He was then referred to a rehabilitation center. Three months later (while still on mifamurtide treatment) he began complaining of pain in his right thigh and hip. FDG PET-CT scan detected a hypermetabolic mass in the proximal right femur and few hypermetabolic lymph nodes in the pelvis. Open biopsy of the mass in the proximal right femur was consistent with osteoblastic osteosarcoma relapse. Next Generation Sequencing performed on the biopsy tissue detected RB mutation in 60% of the tumor cells. With no targeted therapy available, we started second line treatment with Ifosfamide (1.8 g/m^2/day) and Etoposide (100 mg/m^2/day) with plan for surgical resection when possible. CT scan prior to surgery demonstrated a progressive disease involving his right femur. He underwent right hemipelvectomy with right leg amputation. Few regional suspected lymph nodes were sampled. Pathologic examination revealed 50% necrosis of tumor tissue with no involvement of the sampled lymph nodes. One month post-surgery, a follow-up FDG PET-CT scan demonstrated miliary spread of metastatic lesions in both lungs. Treatment was then switched to bevacizumab (10 mg/kg/dose) and PEGylated liposomal doxorubicin (50 mg/m^2). After 4 courses, he suffered from a severe palmoplantar erythrodysesthesia. As a result, treatment with PEGylated liposomal doxorubicin was stopped. Later, while on bevacizumab alone, FDG PET-CT scan revealed progressive disease in the pelvis with spontaneous pneumothorax in the right lung (which resolved spontaneously later). Treatment with PEGylated liposomal doxorubicin was ceased. His treatment regimen was switched to docetaxel (100 mg/m^2/dose on day 8 of each cycle), and gemcitabine (1000 mg/m^2 days 1 and 8 of each cycle) [20]. Bevacizumab (15 mg/kg/dose) was resumed. Simultaneously we started radiation therapy. Radiologic examinations demonstrated a progressive disease on this

therapy. Three years from his first diagnosis he died from progressive metastatic osteoblastic osteosarcoma.

Results

Our three patients with relapsed osteosarcoma were treated with the combination of bevacizumab and PEGylated liposomal doxorubicin after being heavily pretreated. Two out of three patients are in complete remission for more than 4 years from last relapse (7.6 years for patient-1 and 4.3 years for patient-2), while patient-3 did not respond well to this treatment. Despite reports of a slightly higher risk for any severe adverse event in patients with cancer treated with bevacizumab, our patients tolerated bevacizumab generally well [21]. While one patient suffered from mild proteinuria that resolved with dose/frequency reduction, another patient who received lower doses of bevacizumab (5 mg/kg) did not develop any side effect attributed to this drug. One patient (patient-3) had palmoplantar erythrodysesthesia, a common severe adverse dose-schedule limiting effect of PEGylated liposomal doxorubicin [22]. Notably, none of our patients suffered from cardiac toxicity. See Table 1 for patient characteristics and treatment summary.

Discussion

Treatment of relapsed and metastatic osteosarcoma is still challenging for caretakers and prognosis is dismal. Several second-line therapies have been studied but none has remarkably improved the outcome. In this article 2 of our patients with relapsed osteosarcoma had a good response to combination therapy with Bevacizumab and PEGylated liposomal doxorubicin: One with event-free survival of 7.6 years, and another with event-free survival of 4.3 years on their last follow-up. To the best of our knowledge, this combination has not been previously given to patients with osteosarcoma, even though both drugs have been studied separately. Yet, several reasons led us to use this combination in our patients after several second-line treatments had failed: (1) the reported activity of Bevacizumab in various solid tumors, (2) its pharmacokinetics, (3) the observation that angiogenesis correlated with metastasis and worse prognosis in osteosarcoma, and (4) the significant activity of PEGylated liposomal doxorubicin in solid tumors including soft tissue sarcomas [17].

Dose selection, frequency of administration, and duration of treatment were the main issues to be addressed for each of our patients. For PEGylated liposomal doxorubicin we chose the standard dose given to patients with solid tumor which is 40 mg/m^2/dose every 2 to 4 weeks. It was given until either complete remission was achieved, or alternatively, any of the following occurred: progressive disease, potential cardiotoxic cumulative dose, or severe adverse events. As for bevacizumab, when we reviewed the relevant literature we found a wide heterogeneity in protocols. Phase III trials comparing different doses are rare and mainly *vs.* placebo while direct head-to-head comparison has been performed only once [23]. In most protocols, doses ranged from 5 to15 mg/kg/dose, which are the doses approved by FDA for several cancers. Some protocols used as few as 6 cycles, while others gave as much as 96 cycles. Frequency of administration was usually every 2 to 3 weeks. Our decisions were individualized based on disease status, response to treatment, and adverse events. The doses we used ranged between 5 mg/kg (for patient-1 and patient-2 with microscopic disease) and 10 to 15 mg/kg (for patient-3 with advanced disease). Administration frequency was also adjusted based on disease status and side effects and it ranged from one cycle every 2 weeks to one cycle every 8 weeks. Duration of therapy was the issue of biggest debate. On one hand, we had significant responses with minimal or no side effects in patients who, per the literature, would otherwise have a progressive disease with very high risk of mortality. On the other hand, we always kept in mind the rebound effect of angiogenesis that occurs when bevacizumab treatment is ceased, especially in the context of resistant recurrent high grade osteosarcoma in a vessel-dense organ such as the lungs [24].

Bevacizumab was shown to have no effect on outcome when it was studied in a phase II trial. In addition to frontline chemotherapy (Methotrexate, Cisplatin, Doxorubicin) for patients with localized osteosarcoma [14]. One possible explanation for this discrepancy in results is that our responding patients had minimal/microscopic disease by the time we started our regimen. Patient-1 started receiving the combination therapy with no evidence of macroscopic disease, but she had already suffered few relapses on other treatments. Furthermore, knowing the natural history of osteosarcoma we believe she had other microscopic metastases and the next recurrence was just a matter of time. Patient-2 had clear evidence of having osteosarcoma after his surgery as the pathologic exam demonstrated inked margins of the resected metastasis. Consistent with this hypothesis, the non responding patient had a more advanced disease when he started receiving this treatment. The second possible explanation is the principle of "angiogenic switch". Tumors need to overbalance proangiogenic over antiangiogenic factors to be able to support its growth and metastases, also known as the "angiogenic switch". This phenomenon could explain the efficacy of bevacizumab in metastatic setting only as it has become predominant in the disease natural history [23]. A third explanation could be the difference in the chemotherapy combined with bevacizumab. Studies showed that the concentration of PEGylated liposomal doxorubicin in sarcoma tissue could be 14-fold higher at its peak levels compared to conventional doxorubicin [25]. Theoretically, this could be even higher when combined with bevacizumab, resulting in a much stronger antitumor activity. The fourth possible explanation is the genetic heterogeneity in tumor tissues.

Previous studies suggest success of second-line chemotherapy correlates with good response to first-line chemotherapy [8]. We found no such correlation in our patients. After 3 cycles of frontline chemotherapy, patient-3 (the non-responding patient) had 100% tumor cells necrosis, while patient-2, who responded well to our regimen, only had 85% necrosis in the resected tumor tissue.

Treatment success in our patients was not dose dependent. Patient 3 had no response despite receiving higher doses of bevacizumab (15 mg/kg compared with 5 to 10 mg/kg for the other two patients). Besides having a more advanced disease when started on our regimen, this could also be explained by possible intrinsic or extrinsic resistance to bevacizumab in this patient, and the severe side effect of palmar erythrodysesthesia that forced us to stop treatment with PEGylated liposomal doxorubicin after only 4 cycles [26].

Conclusion

A combination therapy of bevacizumab and PEGylated liposomal doxorubicin could be a potential therapeutic option for relapsed osteosarcoma patients with minimal or residual disease. Further controlled trials need to be carried out to validate these results, determine which patients might have maximum benefit of this combination, identify predictive markers for bevacizumab responsiveness, and set the optimal number of treatment cycles.

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