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OLGU SUNUMU/CASE REPORT

Long term survival in a patient with recurrent metastatic Ewing sarcoma treated with irinotecan and temozolomide

İrinotekan ve temozolomid ile tedavi edilen rekürren metastatik Ewing sarkoma hastasında uzun süreli sağkalım

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Abstract
Ewing sarcoma family of tumor is the second most common bone tumor in children and young adults, after osteosarcoma. Different chemotherapeutic regimens are used in treatment of relapsed/recurrent Ewing sarcoma. Promising results were achieved with combination of irinotecan and temozolomide. Our case was a 13-year-old female with relapsed Ewing sarcoma and after 12 cycles of irinotecan (20 mg/m2/10 days) and temozolomide (100mg/m2/5 days) treatment she had not any complaints, and her radiological lesions remained stable for 66 months. Irinotecan and temozolomide have been used successfully in treatment of relapsed/recurrent Ewing sarcoma, but there is a need for randomized prospective studies with larger patient groups for establishing the efficacy of this treatment protocol.
Key words: Ewing Sarcoma, irinotecan, temozolomide.

Öz
Ewing sarkoma tümör ailesi, osteosarkomdan sonra çocuklar ve genç erişkinlerde en sık görülen kemik tümörüdür. Relaps/rekürren Ewing sarkoma tedavisinde çeşitli kemoterapi rejimleri kullanılır. İrinotekan ve temozolomid kombinasyonu ile ümit verici sonuçlar elde edilmiştir. 13 yaşında kadın relaps Ewing sarkomu olan hastamızın, 12 siklus irinotekan (20 mg/m^2/10 gün) ve temozolomid (100mg/m^2/5 gün) tedavisi sonrası bir şikayeti olmadı ve radyolojik lezyonları 66 ay boyunca stabil kaldı. İrinotekan ve temozolomid relaps/rekürren Ewing sarkoma tedavisinde başarıyla kullanılmıştır, fakat bu tedavi protokolünün etkinliğinin kanıtlanması için daha geniş hasta gruplarıyla randomize prospektif çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Ewing sarcoma, irinotecan, temozolomid.

INTRODUCTION

Ewing sarcoma (ES) is the second most prevalent primary osseous malignancy in children and young adults, which was first described in 1921 by American pathologist James Ewing as a "diffuse endothelioma of bone"[1,2]. Around 70% of ES patients who are younger than 20 years old, also disease has a tendency to metastasis to lungs, bones and bone marrow[3]. Current standard treatment of ES consists of multi-agent chemotherapy, surgical resection and irradiation or combination of these approaches[4].

Different combinations of chemotherapeutic agents are used in recurrent ES. With combination of irinotecan (I) and temozolomide (T) treatment, promising results in recurrent cases were recorded in adults and children with solid tumors[5]. We herein, present a relapsed ES patient who achieved a long-term event-free survival after treatment with 12 cycles of IT regimen.

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CASE

The patient was a 13-year-old female who was admitted to Diyarbakir Children's Diseases Hospital with complaints of pain in the hip and shortness of breath. In physical examination, we noted tachycardia and bilateral reduction in breath sounds. A computed tomography (CT) of the chest revealed multiple bilateral hypodense mass lesions with a maximum diameter of 6 cm in the lungs. Bone scintigraphy showed an increased osteoblastic activity in both proximal humeri, both acetabula and right iliac bone. Magnetic resonance imaging of the left knee demonstrated no evidence for recurrence.

In patient's history, left knee was amputated 5 years ago in another center. Before the operation, patient has been treated with neoadjuvant chemotherapy including vincristine, actinomycin D, cyclophosphamide, ifosfamide and etoposide (VAC-IE). Due to the lack of patient's adherence, treatment could not be followed as it was planned. 2 years after quitting the treatment, patient was admitted to the same clinic with more severe pain and swelling in the left knee. Patient's left knee was amputated after administering 3 cycles of VAC-IE neoadjuvant chemotherapy regimen. After the operation, 12 courses VAC-IE regimen were planned to be administered over 51 weeks. Chest CT of the patient disclosed a lymph node of 8 mm in diameter in the right hilar region that was considered to be a metastasis. Thereafter, patient was given 2 cycles of VAC-IE regimen with mesna (1800mg/m2/5 days) and 8 mg dexamethasone.

In our center due to relapse, previously planned 12 cycles of VAC-IE adjuvant chemothreapy regimen was terminated and changed to IT regimen as follows irinotecan (20mg/m2/10 days) via IV route and temozolomide (100mg/m2/5 days) via PO route, one hour prior to irinotecan administration. This combination was considered one cycle of therapy. IT chemotherapy regimen was planned to be administered once every 3 weeks for a total of 12 cycles.

After taking the second IT cycle, in physical examination of the patient, respiratory sounds were normal. Additional evaluation with CT of the chest revealed multiple bilateral metastatic lesions with a maximum diameter of 5 cm in both lungs. Decrease in mass sizes was regarded as a response to the treatment. After receiving seventh IT cycle, patient had no complaints, and her condition was evaluated with chest CT, which showed minimal regression in metastatic lesions in both lungs. These results were recorded as a response, therefore IT regimen was continued. Positron emission tomography-computed tomography scan that was performed after the last IT cycle showed multiple metastatic lesions in both lungs. Accordingly, the patient received external beam irradiation at a dose of 30Gy/21 days to the right lung and mediastinum from both areas. Since patient complained of pain in the hip during the irradiation treatment, bone scintigraphy was performed. Analysis of bone scintigraphy results revealed increased osteoblastic activity in the frontoparietal area, right iliac bone, right acetabulum and also right sacroiliac joint. Therefore, the patient received external beam irradiation at a dose of 30Gy/21 days to the right acetabulum and right femur. Control chest CT revealed a minimal decrease in the size of the metastatic lesions in the both lungs. This was noted as a partial response to the treatment. Subsequently, second control chest CT was performed four months later which revealed a decrease in the size of mass in the basal posterior of both lungs. In addition, multiple air cysts were detected in the posterior of upper lobes, the medial of middle lobe of the right lung, the inferior lingular segment and inferior lobe of posterobasal segment of the left lung (Figure 1 and 2). Furthermore, control bone scintigraphy did not reveal any pathological sign. The patient's status was followed for 66 months, and no complaints were received. To date metastatic lesions are being continuously monitored radiologically in a stable manner.

DISCUSSION

ES is the second most common bone tumor that affects children and young adults. Patients older than 5 and younger than 25 years of age constitute 90% of all ES cases. The incidence of ES is reported 2.93 cases in one million[2]. ES is of aggressive type with tendency to local recurrence and metastasis. About 25% of ES patients are found to have metastasis at the time of diagnosis, and approximately 30% of patients that were diagnosed with localized ES are expected to relapse[6,7]. Interestingly, our patient had multiple metastases in both lungs and the coxae, she did not show any sign of local recurrence.

Although about two-thirds of ES patients with localized tumors were reported to be cured with

standard therapies, survival rate of metastatic ES patients still remains less than 30%[6,7]. In addition, with standard therapies, survival rate of recurrent ES patients is reported to be below 20%[7]. Standard therapy that we followed in our case did not improve patient's condition, however IT treatment initially stabilized our patient's condition and over the course of treatment it showed very promising results. Distant metastasis most commonly involves the lungs (38%), bone (31%), and bone marrow (11%)[8]. In accordance with the literature, bone metastasis was the second metastatic site after lung metastasis in our patient. ES patients who develop lung metastasis have a better prognosis than the ones who develop extra-pulmonary metastasis[9]. Prognosis in patients with relapsed ES is thought to be dependent on the time of the relapse after the initial diagnosis. That is, relapse after two years of diagnosis is not associated with poor prognosis[10]. Similar to what was reported in the literature, our patient also relapsed two years after the initial diagnosis with multiple lung metastases. However, having bone metastasis did not exacerbate her prognosis.

Current standard treatment plans utilize induction chemotherapy followed by local control via surgical resection and/or irradiation and adjuvant chemotherapy[4]. In case of our patient, bone metastases responded well to irradiation treatment, lung metastasis required combination of irradiation and chemotherapy. In patients with lung metastasis, surgical removal of metastatic masses after chemotherapy, and whole lung irradiation, may confer a survival advantage. Use of lung irradiation in children with lung metastasis is reported to diminish the incidence of local recurrences and improve overall relapse-free survival rate[11]. Since the metastatic lesions were in close proximity with vital organs, surgical removal could not be performed. Thus, irradiation treatment was chosen as the most suitable approach. However, it is also reported that the irradiation therapy may result in complications such as secondary malignancies, pathologic fractures, wound complications, pulmonary fibrosis, neuropathy, limb leg discrepancy and femoral head necrosis long term survivors[12].

In patients with disease recurrence, doxorubicin therapy is no longer feasible due to complications caused by administration of cumulative doses administered in the first-line therapy. Chemotherapy regimens used in relapsed ES patients are not standardized and commonly include combinations of alkylating agents and topoisomerase inhibitors (eg., ifosfomide/etoposide, cyclophosphamide/topotecan, or irinotecan/temozolomide). IT drug combination has been used with promising outcomes for several relapsed adult and pediatric solid tumors in recent years [13]. A median time-to-progression of 8.3 months was reported for patients with relapsed or refractory Ewing tumors treated with IT[5]. Maximum tolerated dose of temozolomide combined with protracted irinotecan for pediatric patients with refractory solid tumors demonstrated to be temozolomide 100mg/m^2/day x 5 and irinotecan 10mg/m^2/day [(daily x 5) x 2] every 28 days[14]. Advanced ES patients who were treated with this regimen showed overall 29-60% response rates to this particular treatment[15].

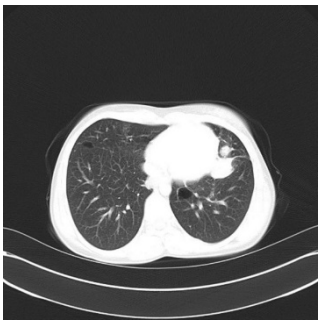

Figure 1. Contrasted CT image showing nodular lesion in basal posterior of left lung and air cysts in both lungs.

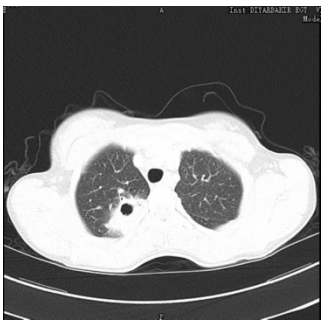

Figure 2. Contrasted CT image showing air cyst in upper posterior of right lung.

Treatment of advanced ES patients with IT combination has shown promising results. Further studies are required to determine its applicability in newly diagnosed patients and also in patients with multiple metastases.

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