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CASE REPORT
OLGU SUNUMU

The Efficacy of Pazopanib in Ewing Sarcoma

Ewing Sarkomunda Pazopanib'in Etkinliği

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ABSTRACT

Ewing sarcoma is the second most common bone cancer in children, and is an aggressive bone and soft tissue cancer in children and young adults. Extraosseous tumors account for approximately 20% of all tumors, with the pelvis being the most commonly affected bone. The 5-year overall survival rate for localized cancer treated with a multimodal approach such as chemotherapy, radiotherapy, and surgery is 70%, but it is less than 30% for metastatic cancer. Poor prognostic factors include pelvis or sacrum primary localization, age over 18, large tumor size, and elevated lactate dehydrogenase levels. Pazopanib's therapeutic effect in the treatment of metastatic extraosseous Ewing sarcoma is unknown. There are only a few case reports about the effectiveness of pazopanib. We present a case of metastatic extraosseous Ewing sarcoma that was successfully treated solely with pazopanib for 8 years without chemotherapy.

Keywords: Ewing Sarcoma, pazopanib, treatment outcome

ÖZ

Ewing sarkomu çocuklarda en sık görülen ikinci kemik kanseri ve çocuklarda ve genç yetişkinlerde agresif bir kemik ve yumuşak doku kanseridir. Ekstraosseöz tümörler tüm tümörlerin yaklaşık %20'sini oluşturur ve pelvis en sık etkilenen kemiktir. Kemoterapi, radyoterapi ve cerrahi gibi multimodal bir yaklaşımla tedavi edilen lokalize kanser için 5 yıllık genel sağkalım oranı %70'tir, ancak metastatik kanser için bu oran %30'dan azdır. Kötü prognostik faktörler arasında pelvis veya sakrum primer lokalizasyonu, 18 yaş üstü, büyük tümör boyutu ve yüksek laktat dehidrogenaz seviyeleri yer almaktadır. Pazopanib'in metastatik ekstraosseöz Ewing sarkomu tedavisindeki terapötik etkisi bilinmemektedir. Pazopanibin etkinliği hakkında sadece birkaç vaka raporu bulunmaktadır. Bu yazıda, kemoterapi uygulanmaksızın 8 yıl boyunca sadece pazopanib ile başarılı bir şekilde tedavi edilen metastatik ekstraosseöz Ewing sarkomlu bir olgu sunulmuştur.

Anahtar Kelimeler: Ewing Sarkomu, pazopanib, tedavi sonucu

INTRODUCTION

Tumors in the Ewing sarcoma family include Ewing sarcoma (ES), peripheral neuroectodermal tumor (PNET), malignant small cell tumor of the thoracopulmonary region (Askin's tumor), and atypical ES. Because they have similar histopathological and immunohistochemical staining patterns, they are thought to have originated from a single mesenchymal progenitor cell; they also share a common chromosomal translocation (1). The most commonly affected region is the pelvis, followed by the axial skeleton and the femur. Patients present to the clinic with localized swelling and pain, and the majority of patients treated have local recurrence (2). The 5-year overall survival rate for localized cancer treated with a multimodal approach such as chemotherapy, radiotherapy, and surgery is 70%, but it is less than 30% for metastatic cancer (3). In a children's oncology group study, adverse factors included pelvic origin, age over 18 years, tumor size greater than 8 cm, and chemotherapy without ifosfamide/etoposide (IE) (4). The standard treatment for ES is vincristine, doxorubicin, cyclophosphamide (VAC), and IE. VAC/IE for 4-6 cycles preoperatively or before local treatment, then VAC/IE for 14-17 cycles is administered for patients with local presentation (5).

CASE REPORT

A 23-year-old woman presented to our clinic in 2014 with complaints of leg pain, abdominal pain, and an inguinal mass. A mass in the pelvis was discovered using abdominal ultrasonography imaging. 18 FDG-PET/CT imaging revealed a 16x13x17.5 cm mass in the pelvis

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that was destroying the right iliac bone, sacrum, and descending to the right acetabulum. Pathology of a trucut biopsy of the mass revealed small round cells with scant cytoplasm; immunohistochemical staining revealed CD 99 positivity and pan CK, EMA, vimentin, chromogranin, synaptophysin, CD 56, and LCA negativity (**Figure 1**).

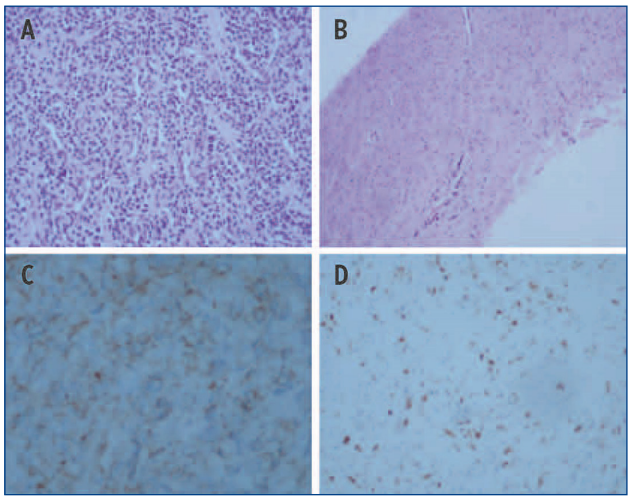

Figure 1. (A) Oval-round shaped hypercellular area consisting of cells with narrow cytoplasm (x20, H&E), **(B)** Area in chondroid structure observed as tumor continuity (x10, H&E), **(C)** Positive staining with CD99 (x40), **(D)** Positive staining with Desmin (x40)

FISH analysis revealed a t(11,22) (q24,p12) fusion transcriptor gene, EWSR 1- FLI1. A VAC/IE chemotherapy regimen of four cycles was planned preoperatively. After four cycles of chemotherapy, 18 FDG-PET/CT imaging revealed stable disease pattern. A multidisciplinary tumor board made the decision to operate on the patient. However, the patient refused the operation. She refused further chemotherapy. Radiotherapy was applied to the pelvic primary tumor. After 6 months of follow-up, a left supraclavicular metastatic lymph node was detected. Biopsy revealed Ewing sarcoma metastasis. Pazopanib 800 mg/day was started orally. After three months, 18 FDG-PET/CT imaging revealed that the primary and the metastatic mass had metabolic response and there were no new lesions. She used pazopanib for 4 years with effective control of the metastatic disease. She stopped using the drug and after 4 months a new 2 cm diameter mass in the lung and new mediastinal lymph nodes thought to be metastatic were detected by contrast-enhanced tomography.. Trucut biopsy of the mass in the lung revealed Ewing sarcoma metastasis. Pazopanib was started again and the metastatic disease was stable after the re-initiation of pazopanib. She was treated with pazopanib 800 mg/day for 4 more years. The only side effect of this long usage of pazopanib was skin depigmentation. She admitted to the emergency clinic with headache and dizziness. Magnetic resonance imaging revealed a 3 cm mass in the occipital lobe. Palliative radiotherapy was applied to the brain metastasis. She refused intravenous chemotherapy. Oral temozolomide was begun. The patient provided informed consent.

DISCUSSION

The cell of origin in ES is thought to have neuroectodermal origin. Almost all cases show reciprocal translocation, including the EWSR 1 gene on chromosome 22. Even if the disease is localized, ES is considered a systemic disease because the majority of patients who do not receive systemic intensive chemotherapy will develop metastases within a year. After receiving localized radiotherapy, our patient refused systemic chemotherapy. Pazopanib 800 mg/day was prescribed to the patient. Pazopanib is a multitargeted tyrosine kinase inhibitor that is taken orally and is approved for the treatment of soft tissue sarcomas other than gastrointestinal stromal sarcoma and liposarcoma. The precise mechanism of action of pazopanib in soft tissue sarcoma is unknown. There are only a few case reports in the literature about the effect of pazopanib in ES patients, and the progression-free survival reported in those studies was only a few months. In our case, the patient has been responding to pazopanib for nearly 8 years.

CONCLUSION

Pazopanib can be used for years with tolerable side effects. It is not known which patients will benefit from pazopanib; a marker or clue is needed for patient selection. For further proof of clinical benefit in patients with soft tissue sarcoma, controlled randomized clinical trials with pazopanib are required.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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