OLGU SUNUMU CASE REPORT

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Cetuximab Treatment for Head and Neck Skin Cancer in a Patient with Heart Transplantation

Kalp Nakilli Bir Hastada Baş-Boyun Cilt Kanseri Tedavisinde Setuksimab Kullanımı

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ABSTRACT The squamous cell skin cancer is the most frequent cancer type in solid organ transplant recipients in the post-transplant setting. A 67 years old male patient who underwent heart transplantation, referred to an oncology clinic with a tumor on the left side of the neck in 2015. The patient underwent surgery includes parotidectomy and functional neck dissection. After the recurrence and two lines of treatment failure, as a third line chemotherapy regimen weekly Cetuximab and Fluorouracil (CF) was started. After three cycles of CF treatment visual and radiological partial response was observed. Metastatic or recurrent head and neck squamous cell carcinoma of the skin is an insistent disease especially in specific conditions like immunosuppression and solid organ transplantation. After the failure of surgery, radiotherapy and platinum-based treatment in our patient; cetuximab plus 5-FU was given as the third line treatment. Our current knowledge, our case is the first cardiac transplant patient who is treated for squamous cell skin cancer with cetuximab. In this specific heart transplanted patient population, cetuximab must be considered as an effective and safe treatment.

Keywords: Cetuximab; skin cancer; heart transplantation

ÖZET Cildin yassı hücreli kanseri transplantasyon sonrasında organ alıcılarında en sık rastalanan kanser tipidir. Altmış yedi yaşında kalp nâkili bir erkek hasta 2015 yılında boynun sol yanında hızlı büyüyen bir tümör ile onkoloji kliniğine refere edilmiştir. Hastaya fonksiyonel boyun disseksiyonunu da içeren paratidektomi uygulanmıştır. Hastalığın nüksü ve iki sıra tedavisinin ardından; hastaya 3. sıra tedavi olarak haftalık setuksimab ve fluorourasil (SF) tedavisi başlanmıştır. Hastada 3 kür SF kemoterapi uygulaması ardından görsel ve radyolojik kısmi yanıt elde edilmiştir. Metastatik ve rekürren baş ve boyun yerleşimli yassı hücreli cilt kanserinin tedavisi immunsupresif ve organ transplantlı hastalarda oldukça zorlayıcıdır. Hastamızda cerrahi, radyoterapi ve platin bazlı tedavilerin başarısız olduğu durumda, 3. basamak tedavide setuksimab ve 5-FU tedavisi uygulanmıştır. Hastamız, literatür taramamıza göre, kalp nakli sonrası yassı hücreli cilt kanserinin setuksimab ile tedavi edildiği ilk olgudur. Bu spesifik kalp nakilli hasta popülasyonunda setuksimab etkili ve güvenli bir tedavi olarak akılda tutulmalıdır.

Anahtar Kelimeler: Setuksimab; cilt kanseri; kalp transplantasyonu

In the last thirty years with revolutionary advancement in immunosuppressive medications and surgical technics, organ transplantation is increased prominently. The new immunosuppressive drugs have decreased graft rejection rates and prolonged patient survival in the last decade. Particularly long-term exposure to combined immunosuppressive therapies (eg. cyclosporine, tacrolimus, azathioprine) brought new problems in this era. Especially increased rates of chronic infections and cancers

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are most challenging parts of these complications. Squamous cell skin cancer is the most frequent cancer type in solid organ transplant recipients in the post-transplant setting.[1] The incidence of the non-melanoma skin cancers in transplant patients is nearly 25 fold higher than the normal population. However, there is no data available for the frequency of the skin cancers in cardiac transplant patients.[2] The main factor is determined as ultraviole (UV) exposure which causes the cutaneous carcinogenesis.[3] In transplant patients, inflammatory response to the tumor is mostly inadequate which make these tumors mostly disguised. Invasive squamous cell carcinoma of the skin may progress rapidly due to reduced inflammatory response.[4] There are some clinical factors which may raise the recurrence and metastasis risk of these tumors. These risk factors include perineural or angiolymphatic invasion, poor differentiation, immunosuppression, origination from a chronic wound or scar and being longer than 2 cm in any dimension.[5-7]

In the transplant patients, strong immunosuppression is the key factor for the disease recurrence and metastasis. Platinum-based chemotherapy regimens are usually used in this setting by the oncologists. The low response rates to these regimens and the increased nephrotoxicity especially in renal transplant patients direct oncologists to new chemotherapy regimens.[8] The epidermal growth factor receptor (EGFR) is known to be over-expressed in squamous cell skin cancer of the head and neck.[9] EGFR is a member of the tyrosine kinase growth factor receptor family which located on the surface of the cell membrane. The EGFR plays a critical role in cancer cell proliferation, metastasis, angiogenesis, and resistance to apoptosis.[10] Cetuximab is a human/murine chimeric antibody that inhibits the EGFR and prevents tumor growth/metastasis.[11] In this article, we represent a heart transplant patient who was treated successfully with cetuximab.

CASE REPORT

A 67 years old male patient, underwent heart transplantation in 2006 due to heart failure, referred to an oncology clinic with a tumor on the left side of the neck in 2015. The biopsy of the mass on the neck was reported as primary squamous cell carcinoma of the skin. On his medical history, he had an acute rheumatic fever in childhood period which had caused heart failure due to valvular insufficiency. In 2012 he was treated with local excisions for squamous cell carcinomas of the skin on his forehead and nose wing. The patient was using tacrolimus and mycophenolate for immunosuppression. There was no other systemic disease on his medical history.

On his first admission to oncology clinic; a squamous cell carcinoma of the skin on the left parotid lodge was detected in physical examination. PET-CT which was performed for distant metastasis suspicion resulted in the absence of metastatic disease. The patient underwent surgery, included parotidectomy and functional neck dissection. The pathology specimen was reported as 3 cm diameter and moderately differentiated squamous cell carcinoma of the skin. The margins were also reported tumor free and three lymph node metastases detected in 30 lymph nodes. After surgery concurrent weekly cisplatin (30mg/m²) and radiotherapy were given as the adjuvant therapy. Six months after the adjuvant treatment, tumor recurrence occurred on the left parotid lodge in June 2016. The patient was considered unsuitable for local ablative treatment options after consultation with ear nose and throat (ENT) and radiation oncology departments. Tacrolimus level of the patient was measured, and he was consulted to the cardiology clinic for systemic chemotherapy. Revision of the immunosuppressant drugs or dose modification was not recommended after cardiologic assessment. He was given modified DCF (Cisplatin 60 mg/m² day 1, Docetaxel 60mg/m² day 1, Fluorouracil 600 mg/m² day 1-5 for 21 days cycles). After three cycles of the mDCF regimen stable disease were observed. Paclitaxel (80 mg/m² for each week) treatment was given to the patient because of intolerance of mDCF regimen. After nine weeks of treatment, PET-CT was performed which showed stable disease. The paclitaxel treatment was continued for six more weeks until new tumors appeared on his left chest skin. As a third line

chemotherapy regimen, weekly Cetuximab and Fluorouracil (CF) (Cetuximab 400mg/m² loading dose, 250mg/m² weekly, 5-FU 1000mg/m² bi-weekly) treatment were given. Two tumors which were located on the left parotid lodge and the left inferior side of the neck appeared before CF treatment (Figures 1, 2).

While his treatment grade 2 dermatological toxicity due to cetuximab developed which resolved with the doxycycline treatment for two weeks. On the fourth cycle (total 10th cycle) of the treatment grade 3 leucopenia was observed related to 5-FU which caused to 20% dose reduction due to the immunosuppressant state of the patient. Tacrolimus levels were monitored closely for interaction with cetuximab during treatment and no toxicity had been observed. After the finish of his treatment for six cycles, cetuximab was continued. The durable response to cetuximab monotherapy was clinically and radiologically seen.

DISCUSSION

Metastatic or recurrent head and neck squamous cell carcinoma of the skin is insistent disease especially in specific conditions like immunosuppression and solid organ transplantation. Platinum-based treatment is the major therapeutic option in this population.[12] Our current knowledge, our case



FIGURE 1: Two tumors located on the left side of the neck before the chemotherapy.



FIGURE 2: The visual response of the tumor after three cycles of chemotherapy.

is the first cardiac transplant patient who is treated for squamous cell skin cancer with cetuximab.

The clinical use of cetuximab depends on mostly case reports, case series and phase 2 trials. In the phase 2 trial, Preneau and her friends reported beneficial effects of cetuximab in squamous and basal cell skin cancer. Twenty-five percent of these patients had immunosuppression. In this trial five patients received cetuximab plus radiotherapy, nine patients received carboplatin plus cetuximab, and six patients have cetuximab monotherapy. The overall response rate on the 9th week of the treatment was 78%. The disease control rate of the combination therapy was better than monotherapy (92% and 50% respectively). The most serious adverse event including grade 3 and 4 hematological was observed in the combination groups.[13] The combination of 5-FU and cetuximab in this setting may be safer than the other combinations. In an article which published by Kalapurakal et al, 8 patients were reported treated with cetuximab. Among 8 patients in this report; 4 had basal cell carcinomas and 4 had squamous cell skin cancers. Complete and partial response rates were 62,5% and 37,5% respectively. The median follow-up of these patients was 17 months. The median disease-free survival of squamous cell skin cancer was much better than basal cell skin carcinoma which was 20,5 months and 1 month respectively.[14]

Trodello and friends compared cetuximab and platinum treatment in a systematic review. Nine patients who were treated with cetuximab had more favorable outcomes than 60 patients treated with platinum-based treatment. The complete remission rates of these patients were 67% and 22% respectively. All of the cetuximab treatment group had a drug-related acneiform rash.[15] Our patient received cetuximab in the third line setting, combined with 5-FU different from the literature. There were no serious adverse events except grade 3 leucopenia and grade 2 acneiform rashes which responsive to doxycycline.

In a recent phase 2 study which was published in 2010, 69% disease control rate, 121 days of progression-free survival and 246 days of overall had been reported with six weeks of cetuximab monotherapy.[16]

After the failure of surgery, radiotherapy and platinum-based treatment in our patient; cetuximab plus 5-FU was given as the third line treatment. On the 9th-week evaluation, partial response was achieved. Grade 3 neutropenia and grade 2 acneiform rash were observed as treatment-related events. In this specific heart transplanted patient population, cetuximab must be considered as an effective and safe treatment. Further clinical investigations are still needed in this group of patients.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mukremin Uysal, Murat Araz;* ***Supervision/ Consultancy:*** *Murat Araz;* ***Source Browsing:*** *İsmail Beypınar, Murat Araz;* ***Written by Makalen:*** *İsmail Beypınar;* ***Critical Review:*** *Murat Araz, Mukremin Uysal.*

REFERENCES

1. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med 2003;348(17):1681-91.
2. Morath C, Mueller M, Goldschmidt H, Schwenger V, Opelz G, Zeier M. Malignancy in renal transplantation. J Am Soc Nephrol 2004;15(6):1582-8.
3. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. J Am Acad Dermatol 2002;47(1):1-17.
4. Mühleisen B, Petrov I, Gächter T, Kurrer M, Schärer L, Dummer R, et al. Progression of cutaneous squamous cell carcinoma in immunosuppressed patients is associated with reduced CD123+ and FOXP3+ cells in the perineoplastic inflammatory infiltrate. Histopathology 2009;55(1):67-76.
5. Veness MJ. Treatment recommendations in patients diagnosed with high-risk cutaneous squamous cell carcinoma. Australas Radiol 2005;49(5):365-76.
6. Krediet JT, Beyer M, Lenz K, Ulrich C, Lange-Asschenfeldt B, Stockfleth E, et al. Sentinel lymph node biopsy and risk factors for predicting metastasis in cutaneous squamous cell carcinoma. Br J Dermatol 2015;172(4):1029-36.
7. Cherpelis BS, Marcusen C, Lang PG. Prognostic factors for metastasis in squamous cell carcinoma of the skin. Dermatol Surg 2002;28(3):268-73.
8. Guthrie TH Jr, Porubsky ES, Luxenberg MN, Shah KJ, Wurtz KL, Watson PR. Cisplatin-based chemotherapy in advanced basal and squamous cell carcinomas of the skin: results in 28 patients including 13 patients receiving multimodality therapy. J Clin Oncol 1990;8(2):342-6.
9. Maubec E, Duvillard P, Velasco V, Crickx B, Avril MF. Immunohistochemical analysis of EGFR and HER-2 in patients with metastatic squamous cell carcinoma of the skin. Anticancer Res 2005;25(2B):1205-10.
10. Castillo L, Etienne-Grimaldi MC, Fischel JL, Formento P, Magné N, Milano G. Pharmacological background of EGFR targeting. Ann Oncol 2004;15(7):1007-12.
11. Harding J, Burtness B. Cetuximab: an epidermal growth factor receptor chemeric human-murine monoclonal antibody. Drugs Today (Barc) 2005;41(2):107-27.
12. Wollina U. Nonmelanoma skin cancer on the rise. J Cutan Aesthet Surg 2012;5(1):11.
13. Preneau S, Rio E, Brocard A, Peuvrel L, Nguyen JM, Quéreux G, et al. Efficacy of cetuximab in the treatment of squamous cell carcinoma. J Dermatolog Treat 2014;25(5):424-7.
14. Kalapurakal SJ, Malone J, Robbins KT, Buescher L, Godwin J, Rao K. Cetuximab in refractory skin cancer treatment. J Cancer 2012;3(1):257-61.
15. Trodello C, Pepper JP, Wong M, Wysong A. Cisplatin and cetuximab treatment for metastatic cutaneous squamous cell carcinoma: a systematic review. Dermatol Surg 2017;43(1):40-9.
16. Maubec E, Petrow P, Scheer-Senyarich I, Duvillard P, Lacroix L, Gelly J, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J Clin Oncol 2011;29(25):3419-26.