doi: 10.53446/actamednicomedia.1640000

Acta Medica Nicomedia

Cilt: 8 Sayı: 2 Haziran 2025 / Vol: 8 Issue: 2 June2025
https://dergipark.org.tr/tr/pub/actamednicomedia

Research Article | Araştırma Makalesi

CETUXIMAB-RELATED SKIN TOXICITY AS A PREDICTIVE MARKER FOR TREATMENT RESPONSE AND PROGNOSIS IN RECURRENT/METASTATIC HEAD AND NECK CANCER PATIENTS TREATED WITH CETUXIMAB AND CHEMOTHERAPY COMBINATION

SETÜKSİMAB VE EŞZAMANLI KEMOTERAPİ İLE TEDAVİ EDİLEN REKÜRREN/METASTATİK BAŞ VE BOYUN KANSERLİ HASTALARDA TEDAVİ YANITI VE PROGNOZ İÇİN PREDİKTİF BİR BELİRTEÇ OLARAK SETÜKSİMAB İLİŞKİLİ CİLT TOKSİSİTESİ

Ilkay Citakkul[1*], Kazim Uygun[1], Yasemin Bakkal Temi[1], Ercan Ozden[2], Umut Kefeli[1], Devrim Cabuk[1], Elif Sahin[3]

[1]Kocaeli University, Faculty of Medicine, Department of Internal Medicine and Medical Oncology, Kocaeli, Türkiye. [2]Pendik Medical Park, Department of Internal Medicine and Medical Oncology, Istanbul, Türkiye. [3]Kocaeli City Hospital, Department of Internal Medicine and Medical Oncology, Kocaeli, Türkiye.

ABSTRACT

Objective: Cetuximab (Cmab),an EGFR inhibitor, is commonly associated with skin toxicity in the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). We aim if skin toxicity can be used as a prognostic sign for Cmab therapy in patients with R/M SCCHN.

Methods: A retrospective review was conducted on demographic data, prognostic features, treatment responses, Cmab-related skin toxicity, and dates of diagnosis, treatment initiation, disease progression, and death for r/mSCCHN patients treated with Cmab at Kocaeli University Medical Oncology Department between 2010 and 2019.The significance of the results has been evaluated by using SPSS (20.0 SPSS Inc., Chicago, IL, USA.) statistical program.

Results: A total of 77 patients were enrolled.A significant association was found between Cmab-related skin toxicity and longer survival in patients with R/M SCCHN. Patients with grade 3 skin toxicity demonstrated prolonged overall survival (OS) and markedly improved progression-free survival (PFS) compared to those without skin toxicity.Additionally, compared to patients without skin toxicity, those with grade 1 or grade 2 skin toxicity had a noticeably prolonged PFS.No significant OS difference was observed between patients with grade 1 or grade 2 toxicity and those without skin toxicity.

Conclusion: Grade 3 skin toxicity correlates with enhanced prognosis, resulting in prolonged OS and PFS. Grade 1 and Grade 2 skin toxicity are associated with improved progression-free survival relative to the absence of toxicity. The data indicate that preventive measures for managing Cmab-related skin toxicity, particularly grade 2 and grade 3, may improve patient outcomes.

Keywords: Cetuximab, head and neck cancer, skin toxicity

ÖZ

Amaç: Rekürren veya metastatik baş ve boyun kanserinde(r/mSCCHN) Setuximab (Cmab) ile ilişkili cilt toksisitesi, tedavide sık görülen bir yan etkidir. Cilt toksisitesinin prognostik bir ölçüt olarak kullanılıp kullanılamayacağını değerlendirmek istedik.

Yöntem: 2010-2019 yılları arasında Kocaeli Üniversitesi Tıbbi Onkoloji Bölümü'nde Cmab ile tedavi edilen r/mSCCHN hastalarının demografik verileri, prognostik özellikleri, tedavi yanıtları, Cmab ile ilişkili cilt toksisitesi, tanı zamanı, tedavi başlama zamanı, progresyon ve ölüm tarihleri retrospektif olarak incelenmiş ve sonuçların anlamlılığı SPSS (20.0 SPSS Inc., Chicago, IL, USA.) istatistik programı kullanılarak değerlendirilmiştir.

Bulgular: Toplam 77 hasta çalışmaya dahil edilmiştir.R/M SCCHN hastalarında Cmab ile ilişkili cilt toksisitesi ile daha uzun sağkalım arasında anlamlı bir ilişki bulunmuştur. Cilt toksisitesi olmayan hastalarda, grad 1 ve grad 2 cilt toksisitesi olanlara kıyasla daha kısa progresyonsuz sağkalım (PFS) görülmüştür. Özellikle, grad 3 cilt toksisitesi olan hastalar, cilt toksisitesi olmayanların yanı sıra grad 1 veya grad 2 toksisitesi olanlara göre daha uzun genel sağkalım (OS) ve daha iyi PFS sergilemiştir. Grad 1 veya grad 2 toksisitesi olan hastalar ile cilt toksisitesi olmayan hastalar arasında anlamlı bir OS farkı gözlenmemiştir.

Sonuç: Özellikle grad 3 cilt toksisitesi , daha uzun OS ve PFS ile yani daha iyi prognoz ile ilişkilidir. Grad 1 ve grad 2 cilt toksisitesi, cilt toksisitesi olmayanlara kıyasla daha iyi PFS ile bağlantılıdır. Bu bulgular, Cmab ile ilişkili cilt toksisitesini, özellikle de grad 2 ve grad 3 cilt toksisitesini yönetmeye yönelik önleyici stratejilerin hasta sonuçlarını iyileştirebileceğini göstermektedir.

Anahtar Kelimeler: Setüksimab, cilt toksisitesi, baş boyun kanseri

***Corresponding author/İletişim kurulacak yazar:** Ilkay Citakkul; Kocaeli University, Faculty of Medicine, Umuttepe Campus, 41001, İzmit/Kocaeli, Türkiye.
Phone/Telefon: +90 (262) 303 75 75, **e-mail/e-posta:** citakkulilkay@gmail.com
Submitted/Başvuru: 14.02.2025 • **Accepted/Kabul:** 08.05.2025 • **Published Online/Online Yayın:** 30.06.2025

Introduction

Squamous cell carcinomas (SCC), which constitute the majority of head and neck cancers, originate from various areas such as the oral cavity, oropharynx, hypopharynx, larynx, and nasopharynx.[1] The incidence of recurrent or metastatic SCC of the head and neck (R/M SCCHN) varies widely across different geographical areas, reflecting regional differences in risk factor exposure. Worldwide, these cancers contribute to over 400,000 deaths annually, with nearly 900,000 new cases diagnosed each year.[2]

Cetuximab, an inhibitor of the Epidermal Growth Factor Receptor (EGFR), has become a key therapeutic option in the treatment of R/M SCCHN. EGFR plays a significant role in promoting cellular growth and maintaining the skin's balance, making cetuximab a critical drug for managing these malignancies.

In treating R/M SCCHN, clinical trials have shown that combination chemotherapy regimens are more effective than single-agent therapies, leading to better survival outcomes. Consequently, combination treatments are the preferred first-line therapy for this patient group.[3-6]

The results of the Phase III EXTREME trial demonstrated that adding cetuximab to a platinum-based chemotherapy regimen (platinum/5-FU) significantly improved both overall survival (OS) and progression-free survival (PFS) when compared to chemotherapy alone, establishing this combination as the standard treatment approach for R/M SCCHN.[7,8]

Despite cetuximab's proven efficacy in R/M SCCHN, most research has focused on its effects in metastatic colorectal cancer, and there is a lack of studies exploring how cetuximab-induced skin toxicity might correlate with prognosis in patients with head and neck cancerThis study seeks to explore the possible link between cetuximab-induced skin toxicity and clinical outcomes, including OS and PFS, in patients with R/M SCCHN at our clinic.

Methods

This retrospective study included patients with R/M SCCHN treated between January 2010 and October 2019, selected from the Oncology Clinic archive at Kocaeli University Faculty of Medicine. Patients who were diagnosed at our hospital but continued treatment at other centers or had inaccessible medical records were excluded.

We analyzed patient data collected from hospital records and from the information system, specifically focusing on those who received Cetuximab, when administered in conjunction with chemotherapy (5-FU/cisplatin or carboplatin/Cmab). The study examinedcomprehensive patient characteristics, including demographics, primary tumor sites, and treatment details.

We also examined the occurrence of skin toxicity associated with cetuximab and the relationship between the severity of skin toxicity and both overall survival (OS) and progression-free survival (PFS). The tumor's site of origin, the initial treatment provided, and the radiological response to the first-line treatment (complete, partial, or stable response) were also assessed.

Inclusion criteria for this study were: (1) a confirmed diagnosis of R/M SCCHN; (2) treatment with cetuximab in combination with chemotherapy at Kocaeli University Faculty of Medicine; and (3) complete availability of clinical and treatment data. Patients were excluded if they: (1) discontinued treatment at our center; (2) had incomplete or inaccessible medical records; or (3) were lost to follow-up before receiving cetuximab treatment.

Skin toxicity was evaluated by both dermatologists and oncologists at Kocaeli University Faculty of Medicine Hospital, using the NCI-CTCAE (Common Toxicity Criteria for Adverse Events, version 4.0) criteria.[9]

Statistical Analysis

The study assessed the correlation between the severity of skin toxicity and extended OS and PFS, without incorporating time-specific criteria. Statistical significance was determined using the SPSS (20.0). Normal distribution was verified through the Kolmogorov-Smirnov and Shapiro-Wilk tests. Numerical data were expressed as mean ± standard deviation, and categorical data were presented as frequency (percentage). Independent sample t-tests were used for group comparisons, while Chi-square analysis assessed categorical variable relationships. Survival analysis was conducted using the log-rank test and the Kaplan-Meier method. A p-value of <0.05 was considered statistically significant.

Ethics Approval

This study received ethical approval from the Institutional Review Board of Kocaeli University (Approval Code: KOÜ GOKAEK-2019/16/09, Project Identifier: 2019/269). All procedures were conducted in compliance with the principles outlined in the Declaration of Helsinki.

Results

This investigation comprised 77 patients, with a median age of 62 years (range: 53-67). Of the patients who experienced recurrence following the initial treatment, 65 (84.4%) presented with metastatic disease, while 12 (15.6%) exhibited locally advanced cancer. Among the metastatic cases, 47 (61%) demonstrated lung metastasis, six (7.8%) exhibited liver metastasis, 15 (19.5%) presented with bone metastasis, and 33 (42.9%) showed mediastinal lymph node metastasis. Patient demographics, including sex, tumor location, disease stage at diagnosis, and initial treatment, were all considered (Table 1).

The distribution of skin toxicity severity was as follows: 32 patients (41.6%) developed grade 3 toxicity, 11 (11.4%) developed grade 2, 11 (11.4%) developed grade 1, and 23 patients (29.9%) exhibited no skin toxicity. In

the progression-free survival analysis, patients with grade 3 skin toxicity had markedly improved survival compared to those without any skin toxicity (log-rank test, P < 0.001), as well as compared to those with grade 1 toxicity (P = 0.003) or grade 2 toxicity (P = 0.001).

Table 1. Patient Characteristics

Patient Characteristics	Number (Number Of Person)	Percentage
Sex		
Male	63	81.8%
Female	14	18.2%
Primary Site		
Oral Cavity	28	36.4%
Nasopharynx	3	3.9%
Oropharynx	2	2.6%
Hypopharynx	9	11.7%
Larenyx	27	35.1%
Sinus	4	5.2%
External Auditory Canal	1	1.3%
Parotid Gland	1	1.3%
Mandibular	1	1.3%
Primary Site Unknown	1	1.3%
At The Time Of Diagnosis		
Local	47	61%
Local Advanced	20	26%
Metastatic	10	13%
The First Treatment Patients Received		
Surgery And Adjuvan RT	38	49.4%
Chemoradiation	20	26%
De Novo Metastatic	10	13%
Surgery	2	9.1%
RT	7	2.6%
Treatment Regimen		
5FU+Cis+Cmab	65	84.4%
5FU+Carbo+Cmab	12	15.6%
Total	77	100%

Both grade 1 and grade 2 skin toxicity were linked to considerably improved PFS when compared to patients who did not exhibit skin toxicity. (Figure 1).

When analyzing the impact of skin toxicity on overall survival, it was clear that patients with grade 3 skin toxicity had significantly longer survival compared to those with no skin issues (hazard ratio, 0.36; 95% CI, 0.19 to 0.66, P < 0.001). In contrast, there was no significant difference in OS between patients with grade 1 or grade 2 skin toxicity and those with no skin reactions. (Figure 2)

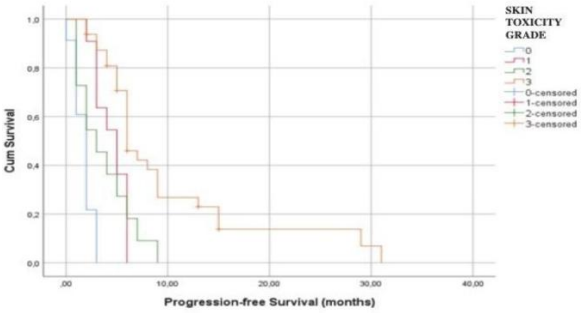

Figure 1. Kaplan-Meier survival curve for progression-free survival in relation to cutaneous toxicity.

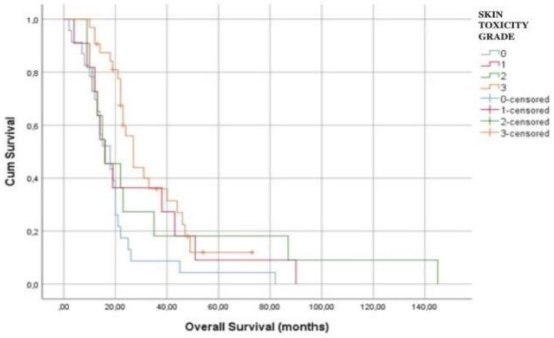

Figure 2. Kaplan-Meier survival curve for overall survival in relation to cutaneous toxicity.

Upon retrospective examination, marked differences in both OS and PFS were detected between patients who developed severe skin reactions (grade 3 toxicity) and those who did not experience any skin complications. Additionally, those with grade 1 or grade 2 skin toxicity had better progression-free survival rates than those who remained free of skin toxicity.

In addition to skin toxicity, several other factors have been evaluated for their potential impact on the prognosis. The analysis revealed that patients with lung metastasis exhibited a mortality risk 2.5 times higher than those without lung involvement (P = 0.18). Age and sex were not significantly associated with mortality (P = 0.73). Furthermore, cachexia was observed to increase the mortality risk by 2.5 times, altough this result was not statistically significant (P = 0.2).

Discussion

Cetuximab plays a significant role in the treatment of R/M SCCHN. Our investigation demonstrated that skin toxicities in cetuximab-treated R/M SCCHN patients may serve as a prognostic indicator of patient survival outcomes. Patients who developed grade 3 skin toxicity exhibited significantly improved overall survival (hazard ratio, 0.36; 95% CI, 0.19-0.66; P < 0.001) and progression-free survival compared to individuals without skin toxicity (log-rank test, P < 0.001), grade 1 (P = 0.003), or grade 2 toxicity (P = 0.001). A study conducted in Japan with 105 patients observed that grade 3 skin toxicity, which developed within 90 days of cetuximab administration, was associated with enhanced survival outcomes[10]. Our findings are consistent with this observation, indicating

that patients who experienced grade 3 skin toxicity demonstrated improved OS and PFS. Although the distribution of skin toxicity was relatively similar in both studies, our cohort had a slightly higher incidence of grade 3 toxicity. These results suggest that skin reactions are not only common treatment-related adverse effects but may also serve as prognostic indicators associated with improved clinical outcomes.

While cetuximab-induced skin toxicity has been extensively investigated in the context of metastatic colorectal cancer, there remains a dearth of data examining its prognostic implications in patients with R/M SCCHN. By demonstrating a correlation between grade 3 skin toxicity and enhanced OS and PFS, our findings suggest that cetuximab-induced dermatologic reactions may reflect not only treatment efficacy, but also serve as a clinically relevant indicator of favorable prognosis in R/M SCCHN.

Cetuximab is generally well tolerated; but cutaneous eruptions, predominantly observed on the facial region, cervical area, scalp, and superior dorsal surface, remain among the most prevalent adverse events. Acneiform rash was the most frequently documented cutaneous reaction in a Japanese study, manifesting in 87% of subjects[10]. Given the established correlation between cutaneous reactions and improved survival outcomes, it is imperative not to prematurely discontinue cetuximab administration in the presence of these adverse effects unless the reactions are of severe intensity. Efforts are underway to develop methods for preventing or minimizing these dermatologic reactions to avoid interrupting treatment. These approaches include recommending mild, hypoallergenic skincare products, using emollients, and protecting patients from sun exposure with high-SPF sunscreen.[11] Nutritional status also plays a key role in managing the side effects of cetuximab, as patients with inadequate nutrition may be more susceptible to complications.[12,13]

Despite advancements in immunotherapy anticipated to confer future survival benefits, current evidence comparing cetuximab-based regimens with immunotherapy for recurrent or metastatic head and neck cancers has yet to demonstrate a clear survival advantage. Cetuximab remains fundamental in the treatment of head and neck tumors owing to its established efficacy and tolerability. Severe cutaneous toxicity associated with cetuximab is a common adverse event and predictive marker for treatment response, providing valuable insights into patient prognosis. Given the prognostic value of skin toxicity in patients receiving cetuximab, earlier consideration of personalized and novel treatment modalities is warranted.

Although our study is constrained by its limited sample size and single-center design, the results imply that cetuximab-induced skin toxicity could serve as a potential indicator of a favorable prognosis in patients with R/M SCCHN. Further multicenter studies involving a larger number of patients are necessary to confirm these findings and investigate their potential clinical significance.

In conclusion, this study provides compelling evidence that cetuximab-induced skin toxicity, particularly grade 3, may serve as a valuable prognostic indicator for patients with R/M SCCHN. The findings demonstrated a positive correlation between severe skin toxicity and improved OS and PFS outcomes. These results are consistent with previous research and underscore the potential dual role of cutaneous reactions as treatment-related adverse effects and indicators of therapeutic efficacy.

Compliance with Ethical Standards

The Institutional Review Board of Kocaeli University granted ethical permission for this investigation (Approval Code: KOÜ GOKAEK-2019, Project Identifier: 2019/269). All procedures were conducted in compliance with the principles outlined in the Declaration of Helsinki.

Conflict of Interest

In this study, there is no conflict of interest with any individual or institution.

Author Contributions

All the authors equally contributed to this work.

Financial Disclosure

None.

References

1. Marur S, Forastiere AA. Head and Neck Cancer: Changing Epidemiology, Diagnosis, and Treatment. *Mayo Clin Proc*. 2008;83(4):489-501. doi:10.4065/83.4.489
2. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5). doi:10.1002/ijc.29210
3. Clavel M, Vermorken JB, Cognetti F, et al. Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group. *Ann Oncol*. 1994;5(6):521-526. doi:10.1093/OXFORDJOURNALS.ANNONC.A058906
4. Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2005;23(15):3562-3567. doi:10.1200/JCO.2005.01.057
5. Jacobs C, Lyman G, Velez-García E, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. *J Clin Oncol*. 1992;10(2):257-263. doi:10.1200/JCO.1992.10.2.257
6. Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. *J Clin Oncol*. 1992;10(8):1245-1251. doi:10.1200/JCO.1992.10.8.1245
7. Guigay J, Aupérin A, Fayette J, et al. Cetuximab, docetaxel, and cisplatin versus platinum, fluorouracil, and cetuximab

as first-line treatment in patients with recurrent or metastatic head and neck squamous-cell carcinoma (GORTEC 2014-01 TPExtreme): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol*. 2021;22(4):463-475. doi:10.1016/S1470-2045(20)30755-5

8. Vermorken JB, Mesia R, Rivera F, et al. Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer. *New England Journal of Medicine*. 2008;359(11):1116-1127. doi:10.1056/NEJMOA0802656/ASSET/A666E058-0210-4F26-B697-A012FB7B4135/ASSETS/IMAGES/LARGE/NEJMOA0802656_T3.JPG
9. Common Terminology Criteria for Adverse Events (CTCAE) | Protocol Development | CTEP. Accessed January 6, 2025. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40
10. Uozumi S, Enokida T, Suzuki S, et al. Predictive Value of Cetuximab-Induced Skin Toxicity in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and NECK. *Front Oncol*. 2018;8. doi:10.3389/fonc.2018.00616
11. Pinto C, Barone CA, Girolomoni G, et al. Management of Skin Toxicity Associated with Cetuximab Treatment in Combination with Chemotherapy or Radiotherapy. *Oncologist*. 2011;16(2):228-238. doi:10.1634/theoncologist.2010-0298
12. Salas S, Baumstarck-Barrau K, Alfonsi M, et al. Impact of the prophylactic gastrostomy for unresectable squamous cell head and neck carcinomas treated with radio-chemotherapy on quality of life: Prospective randomized trial. *Radiother Oncol*. 2009;93(3):503-509. doi:10.1016/J.RADONC.2009.05.016
13. Lee JH, Machtay M, Unger LD, et al. Prophylactic gastrostomy tubes in patients undergoing intensive irradiation for cancer of the head and neck. *Arch Otolaryngol Head Neck Surg*. 1998;124(8):871-875. doi:10.1001/ARCHOTOL.124.8.871