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CASE REPORT

Case Report: Cetuximab use in advanced cutaneous squamous cell carcinoma resistant to chemotherapy [version 1; peer review: 1 approved with reservations]

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Abstract

We present the case of a 60-year-old man with unresectable cutaneous squamous cell carcinoma (cSCC) of the sternal area, which was not amenable to radiation therapy. The treatment history of this patient is remarkable as the disease had progressed through all lines of conventional therapy established in the literature. We decided to initiate treatment with epidermal growth factor receptor (EGFR) inhibitor cetuximab and we reassessed the patient after 12 weeks with a whole-body CT scan, documenting stability in the size and radiologic features of the disease. Cetuximab, like all current treatments for advanced cSCC, is administered off-label and proved effective in preventing further progression of disease in our patient.

Keywords

cutaneous squamous cell carcinoma, cetuximab, EGFR, non-melanoma skin cancer

Open Peer Review

Approval Status

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Any reports and responses or comments on the article can be found at the end of the article.

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Competing interests: No competing interests were disclosed.

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Introduction

This case describes the effective use of cetuximab in an extensive thoracic cutaneous squamous cell carcinoma resistant to all previous lines of chemotherapy.

Non-melanoma skin cancer (NMSC) is the most common malignant neoplasm affecting Caucasian individuals, the main types of which are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). SCC has a lower incidence than BCC and the gold standard of treatment is surgical excision. Between 1–5% of SCCs exhibit biologically aggressive behavior and are resistant to surgery¹.

The management of metastatic or locally advanced SCC includes radiotherapy (alone or in combination with surgery) and systemic chemotherapy, but a consensus for the treatment of cutaneous SCC (cSCC) is still lacking. cSCCs that don't respond to conventional treatments pose a further challenge and may benefit from the use of target therapy, such as inhibitors of the epidermal growth factor receptor (EGFR) pathway and immunotherapy with checkpoint inhibitors².

Cetuximab is a monoclonal antibody first approved for metastatic colon-rectal carcinoma with EGFR expression. EGFR is also overexpressed in the majority of SCCs and the drug is indicated, in association with radiotherapy, for locally advanced head-neck SCC, or with chemotherapy for recurrent/metastatic disease. It is normally used at the standard weekly dosage of 250mg/m². Cetuximab use is currently off-label for cSCC in different skin sites. Current literature supports the use of monoclonal antibodies and oral agents targeting EGFR in advanced cSCC³.

Case presentation

A 60-year-old Caucasian man, currently unemployed, presented to our dermatology department complaining of the recurrence of a thoracic cSCC. Physical examination revealed an extensive ulcerative skin lesion of the sternal area covered by necrotic and fibrinous tissue. The patient reported intermittent pain and bleeding (Figure 1).

The onset of a nodular skin lesion in the same site dated back to 2000, but an initial diagnosis of BCC was made only in 2013, when a single biopsy was performed (see Table 1 for timeline). A computerized tomography (CT) scan followed, demonstrating a high local burden of disease, with destructive osteo-muscular infiltration, preventing a surgical or radiation approach, and the patient was treated with vismodegib (150 mg daily). After 12 months of apparent clinical remission, a local relapse was observed, and the histologic examination of an excisional biopsy diagnosed SCC. Surgical removal of the tumor was not radical, and the patient was referred for adjuvant chemotherapy, failing four consecutive cytotoxic regimens, until the personal decision of the patient to withdraw from treatment. The four regimens were as follows: cisplatin 100mg/m² on day one with fluorouracil 1000mg/m² on days 1–4 of 21-day cycles for three cycles; radio-chemotherapy with gemcitabine 3000mg/m² on days one and 15 of 28-day-cycles; cisplatin 100mg/m² and docetaxel 75mg/m² on day one of 21-day-cycles; and monotherapy with gemcitabine 3000mg/m² on days one and 15 of 28-day-cycles for eight cycles.

A stage III-disease (T3N0M0, Figure 2a)⁴ progressing through several lines of conventional chemotherapy advised the use of targeted and immunological therapies. First, immunohistochemistry for tissue levels of programmed cell death ligand 1 (PD-L1) was performed on the previous biopsy sample documenting no/low expression. We resorted to cetuximab, the use of which is off-label for cSCC. We administered cetuximab at an initial single dose of 400mg/m², followed by 250mg/m² every week, the standard dosing approved for SCC of the head-neck district, for seven cycles and every two weeks for six more cycles. The patient was staged after six and 12 weeks with a whole-body CT scan, documenting stability in the size and radiologic features of the disease. (Figure 2b and 2c).

Therapy with cetuximab is ongoing and we plan to restage the patient after three months. Future management of our patient includes ongoing treatment with cetuximab or evaluation for therapy with programmed cell death protein-1 (PD-1) inhibitors.

Figure 1. Clinical presentation before cetuximab (a) and after six (b) and 12 weeks of therapy (c).

Table 1. Timeline of interventions and outcomes.

Timeline	Medical history and past interventions	
	No family history of skin cancer 1999: total gastrectomy for gastric adenocarcinoma	
	Diagnostic testing and interventions	
Past Interventions 2013 – 2017	2000: Patient reports onset of nodular skin lesion 2013: Incisional biopsy: BCC CT scan (23-Jan-2013): high local burden of disease (5.0cm AP diameter), with destructive osteo-muscular infiltration - <i>vismodegib</i> 150mg daily from Feb to Nov-2013 2014: relapse of nodular skin lesion Excision biopsy (Feb-2014): SCC Wide surgical excision (22-May-2014): not radical Adjuvant chemotherapy: - <i>cisplatin</i> um/ <i>fluorouracil</i> for 3 cycles, Aug – Sep-2014 - <i>radio-chemotherapy with gemcitabine</i> Dec-2014 – Jan-2015 - <i>cisplatin</i> um/ <i>docetaxel</i> Aug-2016 – Nov-2016 - <i>gemcitabine monotherapy</i> for 8 cycles Dec-2016 – Jul-2017	
31-Jan-2018	Baseline assessment	Immunohistochemistry: low/no PD-L1 expression CT scan (31-Jan-2018): 6.2cm AP diameter
19-Apr-2018	Initiation of therapy	- <i>cetuximab</i> initial single dose of 400mg/m ² , then 250mg/m ² weekly
6 weeks	Reassessment	CT scan (28-May-2018): 7.2cm AP diameter - <i>cetuximab</i> 250mg/m ² every two weeks
12 weeks	Final outcome	CT scan (12-July-2018): 7.0cm AP diameter - <i>cetuximab</i> 250mg/m ² every two weeks

AP, anterior-posterior; BCC, basal cell carcinoma; CT, computerized tomography; SCC, squamous cell carcinoma; PD-L1, programmed cell death ligand-1.

Figure 2. CT scan performed at baseline (a), after six (b) and 12 weeks of therapy (c), highlighting the anterior-posterior diameter of the tumor.

Discussion

The results of our report encourage the use of cetuximab in this setting. However, data on long-term efficacy is lacking and we are not able to predict duration of response.

Treatment options for locally invasive or metastatic SCC include systemic chemotherapy, adjuvant chemo-radiotherapy, as well as inhibitors of the EGFR pathway and immunotherapy with

checkpoint inhibitors, which are the latest additions². Systemic drugs for the treatment of cSCC are used off-label and the established regimens, mainly cisplatin-based combinations, are those that were administered to our patient^{5,6}.

Response to second line-therapy, after failure of the first line regimen, is generally uncommon and evidence of prolonged survival is lacking. Prior treatment history, the patient's general

condition and toxicity profiles guide the choice of second-line cytotoxic agent. Gemcitabine has shown activity in previously treated subjects and was employed in our patient with radiotherapy and as single agent⁷.

We were challenged to select an effective treatment in this advanced case and resorted to EGFR inhibitor therapy on the biological notion that EGFR is overexpressed in over 90% of cSCC. A phase II study of unresectable cSCC treated with cetuximab for at least six weeks registered 25% objective response and 42% disease stabilization⁸. Cetuximab is approved for the treatment of locally or regional advanced SCC of the head and neck region (in combination with radiation) or for recurrent or metastatic disease (alone or in association with platinum). Its use in cSCC of other regions is currently off-label but our choice of drug was extensively supported by evidence in published literature³.

A novel attractive approach is immune checkpoint inhibition in the context of cSCC, with monoclonal antibody cemiplimab currently undergoing registration for the treatment of cSCC⁹. Cancer immune surveillance is crucial to the development of cSCC, as demonstrated by the high frequency of cSCC in immunosuppressed patients. PD-1 inhibitors stimulate an anti-cancer immune response and their use in dermatology is established for the treatment of metastatic melanoma. In this case, PD-L1 expression was assessed through immunohistochemistry and low/no expression was found. Mucosal head-neck SCCs display high expression of PD-L1 in the majority of cases¹⁰; however, the role of tumor PD-L1 expression in predicting response to therapy has not been demonstrated and low expression does not contraindicate immunotherapy, even if PD-L1 negative tumors correlate to poorer prognosis and lower response to checkpoint inhibitors.

In accordance with published literature¹¹, we support the necessity of taking serial biopsies of extensive epithelial neoplasms to exclude foci of multiple differentiation and believe that a focus of SCC existed prior to therapy with vismodegib and was responsible for the subsequent recurrence and evolution of disease.

Conclusions

- Serial biopsies are mandatory for advanced BCC candidates prior to vismodegib treatment.
- No drugs are currently approved specifically for cSCC, so all treatments are administered off-label.
- The potential efficacy of cetuximab is based on the biological similarity of cSCC to mucosal SCCs of the head-neck district.
- Low PD-L1 expression does not preclude the efficacy of checkpoint inhibitors.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Grant information

Associazione Romana Ricerca Dermatologica covered the publication fees of this article as support to the authors.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Current Peer Review Status: ?

Version 1

Reviewer Report 03 September 2019

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The case of this 60 y/o man with a history of at least two non-melanoma skin cancers details the use of targeted hedgehog inhibitors for the initial BCC histology followed by cytotoxic chemotherapy and ultimately EGFR directed treatment for what now appears to be cuSCC at the same location. The authors raise the important point of re-biopsy at progression particularly in skin cancers where blended histologies or collision tumors may occur.

The use of Cetuximab has been a strategy for some time. The results outlined here are consistent with what is known—relatively modest clinical value. As referenced, the largest series found a relatively low response rate with modest durations for stable disease. The follow up here is short and the three month assessment is stable disease at best. Thus, the use of Cetuximab is of limited benefit as a single agent.

Anti-PD1 therapy is referenced as an option at progression. For usual advanced cuSCC in elderly not immune suppressed patients, this is actually the preferred first line therapy. The monoclonal Cemiplimab was approved for use in Europe in July of 2019 and prior to that in the US following the NEJM publication by Migden et al July 2018.¹ The field has dramatically changed and the case should be updated to reflect this change. In the absence of a contra-indication of immune therapy, anti-PD1 therapy is standard of care.

It would be very interesting to see an update to this case and the progress of this patient. At that point, the case would provide more information to clinicians.

Specific suggestions:

1. Include the NEJM paper outlining use of Cemiplimab in cuSCC not amenable to curative surgery or radiation.
2. Provide longer follow up than the 12 weeks reported.

3. Outline if the patient was treated with anti-PD1 therapy and why not.
4. Comment on toxicity of therapies.
5. The authors are correct in making the statement that PDL1 testing may not be needed for response to anti-PD1 therapy in this disease. In fact, Cemiplimab is approved without the requirement for testing.
6. If available, it would be interesting to see NGS on the tumor. The tumor mutation burden for cuSCC is very high with some usual mutations (i.e. p53 and NOTCH). As this was a confusion in the case, this data may help clarify the origin of this tumor.

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Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

No

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: I consult for Regeneron and Sanofi who manufacture and market Cemiplimab

Reviewer Expertise: Medical oncology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 03 Dec 2019

Alvise Sernicola, Sapienza University of Rome, Piazzale Aldo Moro 5, Rome, Italy

Dear reviewer,

Thank you for your very accurate review of our paper. We have carefully reviewed all of your suggestions and corrections and revised the manuscript accordingly. Our responses are given in a point-by-point manner below.

We hope the revised version is now suitable for publication and look forward to hearing from you.

Specific suggestions:

1. Include the NEJM paper outlining use of Cemiplimab in cuSCC not amenable to curative surgery or radiation.

Reference to the paper by Migden was added to the introduction: "In 2018, a study by Migden et al. dramatically changed the previous scenario establishing the new standard of care with PD-1 blockade in immune-competent patients, in the absence of contra-indications to immunotherapy (4). Anti-PD1 monoclonal antibody cemiplimab was consequently approved for use in Europe in July 2019."

2. Provide longer follow up than the 12 weeks reported.

We have provided a follow up of up to 80 weeks of treatment with cetuximab as a single agent (54 weeks) and in combination with nivolumab (26 weeks).

3. Outline if the patient was treated with anti-PD1 therapy and why not.

Following progression to stage IV disease during cetuximab therapy, "Combination therapy with the addition of PD-1 blocker was planned and we employed locally available anti-PD1 monoclonal antibody nivolumab according to the following scheme: cetuximab single dose of 250mg/m² Q2W and nivolumab single fixed dose of 240mg Q2W administered at alternating weeks." (case presentation)

4. Comment on toxicity of therapies.

Adverse events to cetuximab has been added to the case presentation: "Therapy was well tolerated, with the only complaint of an acneiform eruption, which began after one week of treatment and was managed with clindamycin 1% gel twice a day and oral minocycline 100mg twice a day for four weeks."

Toxicity has been commented in the discussion: "A diffuse papulopustular acneiform eruption is the most common cutaneous reaction pattern to EGFR inhibitors, reported in over two-thirds of treated subjects but severe in only 5-10% of cases. Cetuximab cutaneous toxicity is suggested to be a proxy for treatment response (10)."

5. The authors are correct in making the statement that PDL1 testing may not be needed for response to anti-PD1 therapy in this disease. In fact, Cemiplimab is approved without the requirement for testing.

Thank you, this has been made explicit in the conclusions: "Low PDL-1 expression does not preclude the efficacy of checkpoint inhibitors; in fact, cemiplimab is approved without requirement for testing."

6. If available, it would be interesting to see NGS on the tumor. The tumor mutation burden for cuSCC is very high with some usual mutations (i.e. p53 and NOTCH). As this was a confusion in the case, this data may help clarify the origin of this tumor.

Thank you for your suggestion, NGS assessment of tumor mutation burden was not available.

Competing Interests: No competing interests were disclosed.

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