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Review Article

Chimeric Monoclonal Antibody Cetuximab Targeting Epidermal Growth Factor-Receptor in Advanced Non-Melanoma Skin Cancer

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Abstract

BACKGROUND: Non-melanoma skin cancer (NMSC) is the most common malignancy in humans. Targeted therapy with monoclonal antibody cetuximab is an option in case of advanced tumor or metastasis.

AIM: We present and update of the use of cetuximab in NMSC searching PUBMED 2011-2017.

METHODS: The monoclonal antibody cetuximab against epidermal growth factor receptor (EGFR) has been investigated for its use in NMSC during the years 2011 to 2017 by a PUBMED research using the following items: "Non-melanoma skin cancer AND cetuximab," "cutaneous squamous cell carcinoma AND cetuximab," and "basal cell carcinoma AND cetuximab", and "cetuximab AND skin toxicity". Available data were analyzed including case reports.

RESULTS: Current evidence of cetuximab efficacy in NMSC was mainly obtained in cutaneous SCC and to a lesser extend in BCC. Response rates vary for neoadjuvant, adjuvant, mono- and combined therapy with cetuximab. Management of cutaneous toxicities is necessary. Guidelines are available.

CONCLUSIONS: Cetuximab is an option for recurrent or advanced NMSC of the skin. It seems to be justified particularly in very high-risk tumors. There is a need for phase III trials.

Introduction

Non-melanoma skin cancer (NMSC) is the most common malignancy in humans, with basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) as the dominant tumor types [1]. As major risk factors the following findings could be identified: age ≥ 50 years of life, Fitzpatrick's phototype I or II, and increased chronic exposure to natural or artificial ultraviolet (UV) irradiation. Other known risk factors include immunosuppression, solid organ transplantation, and use of tanning beds [1][2][3][4][5][6].

Logically, the reduction of UV-exposure seems the major goal in primary prevention [1]. The three pillars of current treatment for localized disease are surgery with wide excision, Mohs surgery for recurrent tumors or special localizations such as the face, and radiotherapy [1].

The role of chemotherapy and targeted therapy in NMSC seems to be confined to advanced cases, where surgery has become impossible or is contraindicated, and to metastatic disease [8][9][10][11][12].

Cetuximab is a chimeric monoclonal antibody against epidermal growth factor receptor (EGFR) and had been FDA-approved for head and neck SCC in conjunction with radiotherapy [12].

We present and update of the use of cetuximab in NMSC searching PUBMED 2011-2017.

BCC

BCC is the most common human cancer. Age-adjusted BCC incidence (cases per 100,000 person-years) was 360.0 in men and 292.9 in women in a recent population-based study in Olsmedt county, Missouri [13]. In contrast to cSCC, BCC does not increase cancer-related mortality [14]. BCC develops as a result of the interplay between ultraviolet radiation (UVR) and genotype with somatic mutations (Smoothed) and germline mutations/polymorphisms. The role of UVR exposure and BCC is not as clear as in cSCC [15].

Prognostic factors of BCCs are tumor size, histological subtype, tumor location, margins, and recurrence. The first line treatment of BCC is wide excision or Mohs surgery dependent on the site of tumor growth. In relapsed tumors, Mohs surgery provides a better outcome with a lower recurrence rate. Radiotherapy is an alternative for patients, who refuse surgery or where surgery is contraindicated. For advanced BCC, Smoothened (SMO) inhibitors vismodegib and sonidegib have been FDA approved [8][9].

Cutaneous SCC

Cutaneous SCC (cSCC) is the second most common NMSC. The age-adjusted cSCC incidence (cases per 100,000 person-years) has been calculated as high as 207.5 for men and 128.8 for women in Olmsted country [13]. The rate of metastasis has been estimated between 1.9 to 2.6%. Risk factors for metastatic spread are the maximum diameter, poor histological differentiation and particular anatomical localizations such as lip, cheek, and ear [16].

The risk of recurrence, metastases, and mortality can be further stratified. High-risk and very high-risk tumors are the possible indication for the use of cetuximab.

High-risk tumors (HRSCC) are characterized by localization in the head-and-neck region, maximum diameter of more than 2 cm, invasion into the subcutaneous adipose tissue, poor differentiation, recurrence or occurrence in a previously irradiated area, and immunosuppression [16].

Very high-risk SCC (VHRSCC) include tumors with perineural, lympho-vascular, parotid, cartilaginous or bony invasion, in-transit, regional or distant metastases [17].

Studies of cetuximab in cutaneous SCC 2011-17

In 2011, the first phase II trial included 36 patients with SCC. Disease control was obtained in 69% after 6 weeks of treatment. Patients received a 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly for at least 6 weeks with 48 weeks follow-up. In this study, three related serious adverse events were observed - two grade 4 infusion reactions and one grade 3 interstitial pneumonitis. Grade 1 to 2 acne-like rash occurred in 78% of patients and was associated with prolonged PFS [18].

Table 1: Results of cetuximab therapy in cSCC 2011-2017 (disease-free survival – DFS, overall survival – OAS, complete response – CR, partial response – PR, stable disease – SD, progressive disease – PD)

No.	Metastases	Best response	Outcome	Remarks	Reference
36	lymph node	2 x CR 8 x PR 15 x SD 6 x PD 5 x not assessable	1 x at 6 months	in part with surgery phase II trial	[18]
1	lymph node	CR after 6 weeks	DFS 7 months	1st line	[19]
1	satellites	CR	> 6 months	plus volumetric modulated arc-radiotherapy	[20]
8	-	3 x CR 2 x PR 1 x PD	3- >21 months 6-18 months	6 x with radiotherapy	[21]
4	2 x lymph node	3 x CR	1 x relapse after 6 months, median disease-free survival 20.5 months		[22]
1	lung, pleura, lymph nodes	PR after 6 months	-	cetuximab plus paclitaxel	[23]
3	-	1 x CR after 16 weeks 2 x PR 1 x PR	DFS 16 months PR for 17 and 18 months died from other reasons		[24]
6	-	3 x CR 2 x PD 1 x intolerance	median 3 years	in combination with surgery VHRSCC	[17]
17	bone or visceral	4 x PR	-	penile & scrotal, cetuximab alone or with cisplatin	[25]
6	all metastatic	67% disease control at 4 to 8 weeks	mean overall survival 25 ± 16.2 months		[26]
1	-	CR	-		[27]

There have been a number of retrospective case series and case reports been published since then (Table 1). Cetuximab has been used as 1st – 3rd line therapy, alone or in combination with surgery, radiotherapy or chemotherapy [17][18][19][20][21][22][23][24][25][26][27].

Cetuximab in advanced BCC 2011-2017

Cetuximab has also been used in patients with advanced BCC [11]. The safety profile is not different from SCC patients. However, Karapurakal et al. (2015) used a lower starting dosage of 125 mg/m^2 increased to 250 mg/m^2 or 300 mg/m^2. Their dosages varied from 125 mg/m^2 once a month to 300 mg/m^2 once a week. The authors did not explain the reason for these dose variations. Two patients achieved a CR, the other 2 had a PR. During a median follow-up of 12 months overall survival was 100%. Mean disease-free survival was one month. Three of their four patients suffered from Gorlin-Goltz syndrome [22].

Management of adverse effects

Skin toxicity is the most common adverse effects of cetuximab. Treatment is based on skin moisturizers and sunscreens [28]. In a retrospective trial on gastrointestinal cancer patients, prophylactic and reactive treatment for acne-like rash was equally effective [29].

Treatment of the papulopustular rash includes topical use of erythromycin or metronidazole for mild cases, and systemic tetracyclines or retinoids for skin toxicities grade ≥2 with temporary interruption of cetuximab therapy [30]. The incidence of skin toxicity seems to be lower in smokers but the incidence of anorexia is higher compared to non-smokers [31].

Topical vitamin K3 (menadione) is not effective in the prevention of cutaneous toxicity nor does it change the expression of EGFR in skin [32].

In conclusion, there are increasingly more data available on the use of targeted therapy in advanced NMSC although controlled prospective, randomized, placebo-controlled phase III trials are still missing. From the available data, cetuximab seems to be effective as monotherapy after surgery. The safety profile is not different from approved indications such as advanced colorectal and head-and-neck cancer. In contrast to hedgehog inhibitor vismodegib approved for advanced BCC, second cSCC have not been observed with cetuximab therapy of NMSC [33][34][35][36].

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