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Treatment of squamous cell carcinoma of the anal canal: A new strategies with anti-EGFR therapy and immunotherapy

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ABSTRACT

The incidence of squamous cell carcinoma of the anal canal (SCAC) is increasing in both sexes but the standard treatment remains that of 20 years ago. However, interesting data have recently emerged on the use of anti-epidermal growth factor receptor (EGFR) agents and immunotherapy in advanced disease. Thus, new avenues of research are opening up that will hopefully lead to more effective therapeutic strategies. We provide an overview of the latest studies published on this tumor and discuss the possible future therapeutic options for combination therapy, anti-EGFR treatment and radiotherapy.

1. Introduction

Squamous cell carcinoma of the anal canal (SCAC) represents 2.5% of all gastrointestinal cancers. However, the incidence of this tumor is gradually increasing in both sexes due to infection from human papilloma virus (HPV) (Altekruse et al., 1975). Five-year survival is 80% for localized disease (Johnson et al., 2004). In the past, abdominoperineal resection and permanent colostomy was the standard therapy for non-metastatic disease and 5-year survival was 50–60% (Clark et al., 2004). In 1974 Nigro et al. (1974) reported a complete response (CR) in 3 patients treated with a combination of radiation therapy and chemotherapy (mitomycin C and 5-fluorouracil [5-FU]). However, no phase III randomized trials comparing abdominoperineal resection with radiochemotherapy have been conducted to date. Furthermore, there are virtually no data in the literature on the treatment of metastatic SCAC, the current standard of care for which is cisplatin and 5-FU (Faivre et al., 1999; Jaiyesimi and Cisplatin, 1993; Tanum, 1993; Khater et al., 1986; Ajani et al., 1989). The overall response rate is 60%, with a median survival of 12 months. As with localized disease, treatment for advanced disease has not changed in the last 20 years. However, several interesting studies have been published in this area over the past 12 months. The present review evaluates the latest data published on SCAC and discusses the future therapeutic options for combination therapy, anti-EGFR treatment and radiotherapy.

2. Role of anti-EGFR therapy in the treatment of SCAC

Epidermal growth factor receptor (EGFR) is overexpressed in about 90% of SCAC, whereas KRAS and NRAS mutations are rare (Capelli et al., 2016; Casadei Gardini et al., 2014; Zampino et al., 2009; Cacheux et al., 2016). PIK3CA is mutated in 20% of patients (Capelli et al., 2016). These observations provide a theoretical rationale for integrating anti-EGFR agents into standard treatment for SCAC. Fig. 1 summarizes the chemoradiotherapy schedules of the most important studies carried out to date and Table 1 reports the main results obtained. In 2013, Olivatto et al. were the first to evaluate the use of cetuximab (Olivatto et al., 2013) in a phase I study in which cetuximab was administered with cisplatin and 5-FU in concomitance with radiotherapy. The study was closed due to challenging safety results. All 23 patients enrolled experienced grade 3/4 toxicity (100%): radiation dermatitis in 52.1% of cases, diarrhea in 43.4%, thrombosis and embolism in 26% and infection in 21%. With regard to efficacy, encouraging results were reported, with 95% of patients achieving a pathological CR and a 3-year locoregional control rate of 64.2%. In the same year, Deutsch et al. published the results of the UNICANCER ACCORD 16 phase II trial (Deutsch et al., 2013) in which the same regimen was used to treat 16 patients. However, the study was prematurely closed because of severe toxicity in 88% of the population. With regard to efficacy, 55% of patients showed a CR and 45% a partial response (PR). Median objective response duration was 14.7 months.

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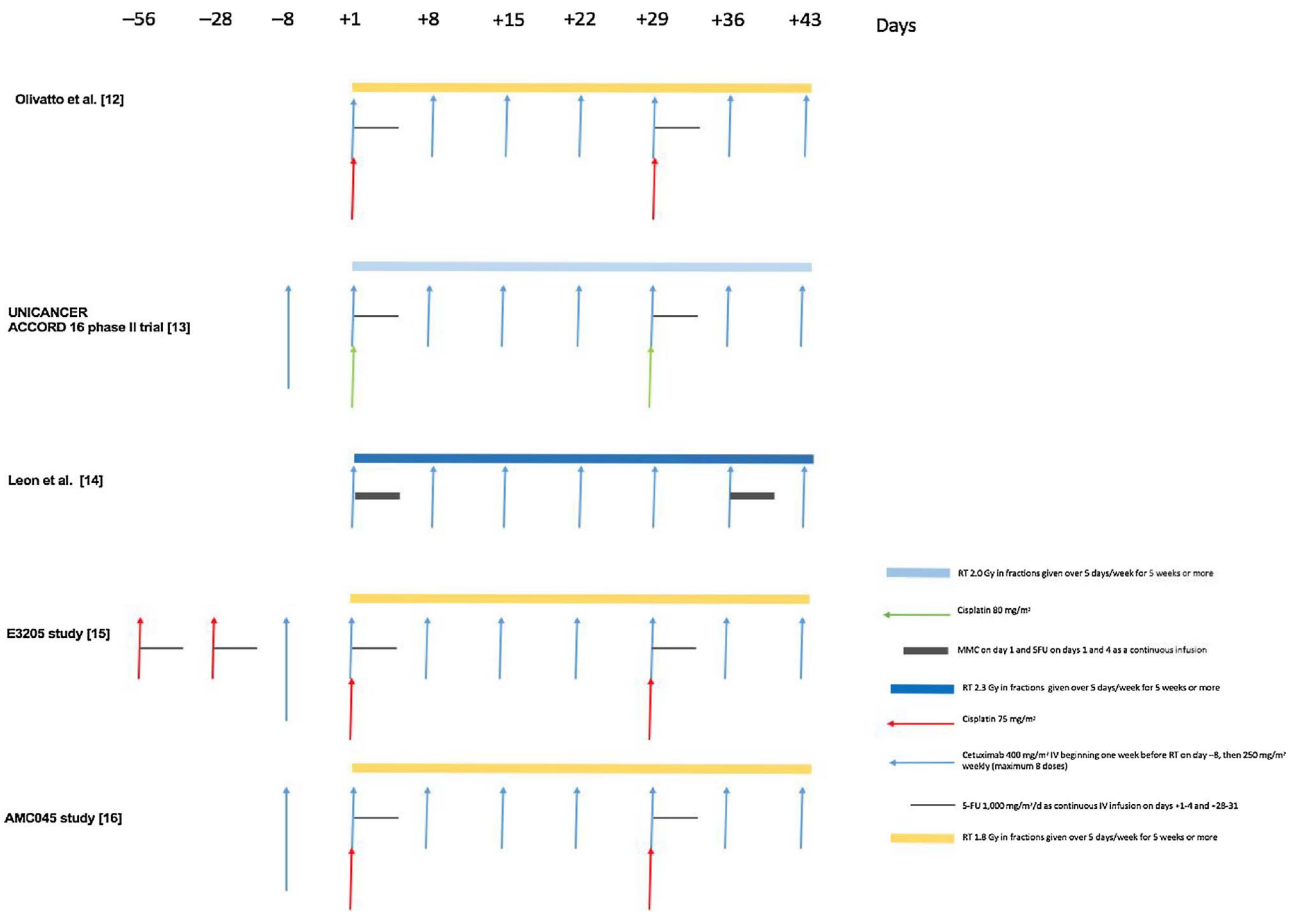

Fig. 1. Treatment scheme of the most important studies on SCAC. 5-FU, 5-fluorouracil; IV, intravenous; RT, radiation therapy; MMC, mitomycin C.

Table 1
Results from the most relevant studies with anti-EGFR antibodies on SCAC.

	Grade 3/4 adverse event %	Treatment-related death%	Median objective response (months)	One-year colostomy-free survival%	Complete response%	Partial response%	Locoregional control rate (2-year) (3-year) %	PFS (1-year) (3-year) %	OS (1-year) (2-year) (3-year) %
Olivatto et al.	86	NA	NA	NA	95	NA	(NA)	(NA)	(NA)
							(64.2)	(NA)	(NA) (NA)
Deutsch et al.	88	0	14.7	67	55	45	(NA)	(62)	(92)
							(NA)	(NA)	(NA) (NA)
Leon et al.	81.8	0	NA	NA	91	NA	(73) (NA)	(NA) (NA)	(NA) (88) (NA)
E3205 study	32	5	NA	NA	59	NA	(NA) (77)	(NA) (68)	(NA) (NA) (83)
AMC045 study	26	4.4	NA	NA	62	5	(NA)	(NA)	(NA)
							(58)	(72)	(NA) (79)

SCAC, squamous cell carcinoma of the anal canal; PFS, progression-free survival; OS, overall survival; NA, not available.

38% of patients relapsed after a median follow-up of 22 months. One-year colostomy-free survival was 67%, one year progression-free survival (PFS) was 62% and one-year overall survival (OS) was 92%.

In 2015, Leon et al. (2015) published their findings of a phase I study evaluating cetuximab, mitomycin C and 5-FU in concomitance with radiotherapy. Thirteen patients were enrolled. The most common grade 3 and 4 side-effects were radiation dermatitis in 63% of patients, hematologic toxicity in 54% and diarrhea in 36%. No treatment-related deaths were recorded. Estimated 2-year relapse-free survival (RFS) and OS was 73% and 88%, respectively.

The results from the phase II E3205 study (Garg et al., 2017) were published in March 2017. Patients received cetuximab, cisplatin and 5-FU at the same dosages as those of the aforementioned studies. Of the 61 patients enrolled, 19 (32%) had grade 4 toxicity and 3 (5%) died