Unexpected toxicity of cetuximab combined with conventional chemoradiotherapy in patients with locally advanced anal cancer: results of the UNICANCER ACCORD 16 phase II trial†


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Background: The ACCORD 16 phase II trial aimed to evaluate the objective response rate after combination of conventional chemoradiotherapy (CRT) and cetuximab in locally advanced anal canal carcinoma (LAACC).

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References

Keywords: ACCORD 16 trial; chemoradiotherapy; cetuximab; anal cancer.

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†Presented at the 2011 meeting of the American Society of Clinical Oncology meeting in Chicago.
Patients and methods: Immunocompetent patients with histologically confirmed LAACC received CRT [45 gray (Gy)] in 25 fractions over 5 weeks, fluorouracil and cisplatin during weeks 1 and 5, in combination with weekly dose of cetuximab (250 mg/m² with a loading dose of 400 mg/m² 1 week before irradiation), and a standard dose boost (20 Gy). The trial was originally designed to include 81 patients to detect a 15% of objective response increase with the new combination in comparison with CRT.

Results: The trial was prematurely stopped after the declaration of 15 serious adverse events (SAEs) in 14 out of 16 patients. Five patients received the entire planned treatment, and the compliance was higher after amendments of the protocol. Among the 15 SAEs, 6 were unexpected. Grade (G) 3/4 acute toxic effects, observed in 88% patients, were general (n = 13, 81%), digestive (n = 9, 56%), dermatological (n = 5, 31%), infectious (n = 4, 25%), haematological (n = 3, 19%), and others (n = 9); and three patients suffered from six G3/4 late toxic effects. No treatment-related death was reported. All 11 assessable patients had an objective response consisting of six complete (55%) and five partial (45%) response 2 months after the end of the treatment. Thirteen patients were followed up with a median of 22 months [95% confidence interval (CI): 18–27] and had a 1-year colostomy-free survival, progression-free and overall survival rate of 67% (95% CI: 40%–86%), 62% (95% CI: 36%–82%), and 92% (95% CI: 67%–99%), respectively.

Conclusion: CRT plus cetuximab was unacceptably toxic in this population of patients. Results of others phase II trials evaluating this combination are awaited to confirm these findings.

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Key words: anal cancer, cetuximab, chemoradiotherapy, phase II, targeted therapy, toxicity

Introduction

Combined chemoradiotherapy (CRT) has become a standard treatment of the localized squamous cell anal canal cancer because it is able to cure patients while preserving the anal sphincter. In the three major randomized clinical trials of the United Kingdom Coordinating Committee on Cancer Research (UKCCCR), the European Organisation for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group (RTOG/ECOG), local control (LC) and overall survival (OS) rates were significantly higher for CRT compared with radiotherapy (RT) alone. Furthermore, CRT led to a 32% higher colostomy-free rate, and clinical and pathological complete response (CR) reached 80% and 83%, respectively [1–3].

However, a lower survival and higher local failure rates (25% at 2 years) are reported in patients with advanced tumours (i.e. stage T3–T4 and or positive nodes) [4]. Induction chemotherapy was evaluated in a phase II study of the cancer and Leukemia Group B (CALGB 9281) in 45 patients with locally advanced anal canal carcinoma (LAACC) and resulted in a colostomy- and disease-free rate of 50% [5]. Despite these encouraging results, in the randomized ACCORD 03 trial, intensified CRT with the addition of induction chemotherapy and/or an additional radiation boost failed to increase the colostomy-free survival in comparison with standard CRT [6].

Preclinical evidence suggests that cetuximab, an IgG1 monoclonal antibody that exclusively targets epidermal growth factor receptor (EGFR) with high affinity, has radiosensitizing properties [7]. In patients with locally advanced head and neck cancer, CRT with cetuximab improved LC and OS in comparison with RT alone [8]. Since then, recent phase II studies have shown that addition of cetuximab to platinum-based CRT is feasible, and show promising activity without increasing mortality in various advanced tumour types [9–12]. EGFR expression is common in anal cancer [13]. In preliminary results of a phase I trial evaluating 10 patients with LAACC, the combination of RT [45 gray (Gy) plus a boost of 20 Gy], cetuximab (400 mg/m² on day 1, then seven weekly doses of 250 mg/m²), and a dose escalation of 5-fluorouracil (5-FU) and cisplatin resulted in one grade (G) 4 toxicity (neutropenic fever) only [14]. In the light of these emerging data, the ACCORD 16 phase II trial aimed to evaluate the objective response rate after conventional CRT combined with cetuximab in LAACC patients.

Patients and methods

Eligibility criteria

Eligible patients had histologically confirmed locally advanced [T2 (tumour size >3 cm) to T4 and/or N1–N3] anal squamous cell cancer with measurable disease according to the RECIST criteria. Initial imaging evaluation included an endorectal ultrasonography and a body computed tomography (CT).

All patients were human immunodeficiency virus (HIV)-negative, had World Health Organization performance status of 0 to 2, with no metastatic disease. Other inclusion criteria were age ≥ 18 years, adequate bone marrow, renal and liver function, and a negative pregnancy test. Written informed consent was obtained from each patient before study entry. Patients with other histological subtype or a past medical history including another cancer, previous cancer treatment, or HIV-positive were excluded from the study. The protocol was approved by the Kremlin-Bicêtre ethics committee.

Treatment

Patients received external-beam conformal RT (EBRT) or intensity modulated RT (IMRT) at a total dose of 45 Gy in the pelvis, calculated at the International Commission of Radiation Units reference point, at the intersection of the central axes of the beams, in daily fractions of 1.8 Gy, according to EORTC [3] and UKCCCR trials [1]. All fields were treated every day, 5 days per week for a total of 5 weeks. Briefly, IMRT plans were generated using the commercial inverse planning software (Eclipse, Helios, version 7.2.34, Varian, Palo Alto, CA). Beam geometry consisted of seven coplanar fields for the whole pelvis, and a five-field technique was used for the IMRT boost. Patients were treated with an 18-MV linear accelerator with a millennium dynamic multileaf collimator (21EX, Varian, Palo Alto, CA).
results

trial conduct

A total of 16 patients with squamous LAACC were enrolled in the study. Supplementary Table S1, available at Annals of Oncology online, lists the main characteristics of the study population.

Between March and July 2009, 10 patients from six centres were included (first period of inclusion). In September 2009, inclusions were suspended after nine SAEs. Inclusions were resumed after protocol amendments [decreased the dose of 5-FU from 800 to 600 mg/m²/day in continuous infusion; secondary prophylaxis with granulocyte colony-stimulating factor (G-CSF); and mandatory IMRT with a reinforcement of IMRT constraints of the maximal dose allowed to the digestive tract] in January 2010, and six additional patients were enrolled in three centres (second period of inclusion). The inclusions were suspended and the trial was prematurely stopped after the declaration of six new SAEs in September 2010.

treatment delivery and compliance

The median dose delivered was 65 Gy (51.4–65) in 35 fractions (19–36) and 71 days (54–85) with either EBRT (n = 3) or IMRT (n = 11). A brachytherapy boost was administered in two patients. Owing to toxicity, RT was interrupted for a total of 14 days among three patients. Two patients received a total dose of <60 Gy. Data are missing for two patients who withdrew their consent after the first injection of cetuximab (Supplementary Table S2, available at Annals of Oncology online). Data on duration were missing in two other patients with early withdrawal.

Eight patients (50%) received the six planned injections of cetuximab. Three patients received the loading injection of cetuximab only and there were four definitive interruptions of treatment. No dose reduction of cetuximab was observed.

Three patients received 5-FU bolus (800 mg/m²); and three and six patients received continuous 5-FU at a dose of 800 and 600 mg/m²/day, respectively. Two patients received continuous 800 mg/m²/day, as bolus for the first cycle and as continuous infusion for the second one. Two out of five patients (40%) receiving 5-FU bolus at the first cycle and one out of nine patients (11%) receiving continuous 5-FU at the first cycle did not receive the second cycle of 5-FU. Concerning cisplatin, three patients received only the first injection, two had a dose reduction during the second cycle, and one patient received 25% of the dose at each injection.

Overall, five patients received the entire planned treatment. The compliance was higher during the second period of inclusion: six patients received the entire planned treatment, except one dose reduction at the second cycle of cisplatin for one patient, and one non-toxicity-related dose reduction of RT.

toxicity

Fifteen SAEs were observed in 14 out of 16 patients. One patients had two SAEs, and two SAEs were not related to the treatment. There were 6 unexpected SAEs out of 10 SAEs (60%) in the first period of inclusion and no unexpected SAE out of 5 SAEs (0%) in the second period of inclusion.
G3/4 toxic effects were observed in 14 (88%) patients, and all patients but one had treatment-related toxicity. G3/4 acute toxic effects observed were general (n = 13), digestive (n = 9), dermatological (n = 5), infectious (n = 4), haematological (n = 3), and others (n = 9; Supplementary Table S3, available at Annals of Oncology online). No treatment-related death, G3/4 renal failure, or G3/4 anitis and proctitis was reported.

Three patients suffered from six severe late toxic effects. G3/4 late toxic effects observed were G3 abdominal (n = 1) and lumbar (n = 1) chronic pain, cutaneous (G3 acniform eruption, n = 1), G3 mucositis (n = 1), G4 perineal necrosis (n = 1), G3 perineal fistula (n = 1), and G3 febrile syndrome (n = 1).

response and survival
All the 11 assessable patients had an objective response consisting of six complete (55%) and five partial (45%) response and one progression 2 months after the end of the treatment. Median objective response duration was 14.7 months (range: 2.5–24.4).

For the 13 patients with long-term follow-up, the median follow-up was 22 months [95% confidence interval (CI): 18–27]. Among these patients, five had a recurrence (38%), four local, and one distant, at a median time of 8 months (4.5–10). Five patients required a colostomy, due to local recurrence (n = 3) or fistulae (n = 2). Three patients died of their cancer during the follow-up. One-year colostomy-free survival, PFS, and OS rates were 67% (95% CI: 40%–86%), 62% (95% CI: 36%–82%), and 92% (95% CI: 67%–99%), respectively (Supplementary Figure S2, available at Annals of Oncology online).

discussion
The UNICANCER ACCORD 16 phase II trial was prematurely stopped after the declaration of 15 SAEs in 14 out of 16 enrolled patients and a high rate of severe toxic effects (88%). Although the compliance being higher after amendments of the protocol (second period of inclusion), only five patients received the entire planned treatment.

In ACCORD 16, acute side-effects were higher than those previously described in the main randomized phase III trials reporting conventional CRT. In the CRT arms of the UKCCCR [1], the RTOG/ECOG [2], and the ACCORD 03 [6] trials, acute side-effects were 34% (G3/4 or ‘severe’; n = 100/292), 20% (G4/5), and 29% (G3/4; n = 46/157 without patients receiving induction CT but including patients with high-dose RT), respectively. Moreover, here, only 5 out of 16 (31%) patients received the entire planned treatment, whereas 74%–92% received the initially planned concomitant CT and 90%–98% completed RT in the previous studies [1, 2, 6]. Also, given the small size of the population, the short follow-up, and the poor compliance to the treatment, we agree that efficacy results may not be assessable in the present study.

Cetuximab combined with cisplatin/5-FU-CRT is currently evaluated in anal cancer patients in two other phase II trials: ECOG 3205 (immunocompetent) and AIDS Associated Malignancies Clinical Trials Consortium 045 (HIV-positive: AMC045). Patients generally received the same schedule of treatment that was delivered in our study, combining cetuximab (400 mg/m² loading, then 250 mg/m²/week for 6 to 8 weeks) plus cisplatin (75 mg/m², two cycles) and 5-FU (1000 mg/m²/day infusion days 1–4, two cycles) concurrently with RT (45–54 Gy), beginning with the second dose of cetuximab. The patients also received two cycles of cisplatin/5-FU alone before CRT associated with cetuximab, but this was discontinued on the recommendation of the NCI Anorectal Task Force after a trial with 28 patients. The primary end point was the 3-year locoregional failure rate, and the early results on the first 28 patients from E3205 were presented at ASCO 2012 [16]. Severe toxic effects, defined as type I (any G4–5 G4 cardiac) and II (G4 RT skin or diarrhoea), were reported for two patients. This result was comparable with our experience (no G5, or G4 cardiac, skin, or diarrhoea in ACCORD 16). No data was provided on haematological or infectious toxic effects. Similar to the compliance of treatment monitored in the second part of our trial, 79% patients completed the protocol therapy. Anyway, a comparison may not be possible given the preliminary data, the low number of patients, and the difference of population studied (88% of American Joint Committee on Cancer stage III in our study versus 39% in ECOG 3205). Patients in ECOG 3205 also usually received a lower dose of RT (45–54 Gy) than in the present study (65 Gy).

The schedule employed in ACCORD 16 was based on the results of the only one phase I trial reported. There, patients treated with CRT (55 Gy, 5-FU 1000 mg/m²/day and cisplatin 80 mg/m²/day) and cetuximab (400 mg/m² on day 1, then seven weekly doses of 250 mg/m²) did not experience a dose-limiting toxicity [14]. However, no data on the use of G-CSF, dose constraints, and technique of RT employed in ECOG 3205 or the phase I reported by Olivatto et al. [14] were provided. In our trial, 11 out of 16 patients were treated with IMRT and 2 patients received a brachytherapy boost. It is well described that early and late local toxic effects in anal cancer correlate with the clinical stage and the type of technique of RT (including boost) [17]. IMRT appears to be effective and better tolerated than EBRT in the CRT regimen for the treatment of anal canal cancer [18–20]. In a series of 53 patients treated with CRT, including IMRT, Salama et al. [19] observed 15% digestive, 38% dermatological, and 34% neutropenia acute G3/4 toxicity, resulting in treatment breaks in ~40% of patients. However, most of these patients underwent a 5-FU/mitomycin-C-based chemotherapy [18–20]. Although it is matter of debate [21], recent randomized trials confirmed that definitive CRT with concurrent 5FU/mitomycin-C remains the standard of care, compared with 5-FU cisplatin, because it has a statistically significant, clinically meaningful impact on survival with similar toxic effects [22, 23]. Nevertheless, as in the ACCORD 03 trial [6], cetuximab was associated with 5-FU/cisplatin in our analysis. In fact, at the time of the initiation of the study, early uncontrolled French collaborative studies suggested encouraging clinical results with the substitution of cisplatin for mitomycin-C [24].

New early clinical trials, integrating IMRT and evaluating the feasibility of concurrent 5FU/mitomycin-C-based CRT with a range of anti-EGFR therapies (cetuximab: NCT01621217, panitumumab: NCT01285778/NCT01581840, or nimotuzumab: NCT01382745), are in progress. Still, results of ongoing phase II (ECOG 3205 and AMC045) are awaited to
confirm that cetuximab-based CRT is unacceptably toxic in LAACC patients.

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disclosure

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references


