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Mitomycin C with continuous fluorouracil or with cisplatin in combination with radiotherapy for locally advanced anal cancer (European Organisation for Research and Treatment of Cancer phase II study 22011-40014) ☆

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ABSTRACT

Purpose: To assess the feasibility and activity of radio-chemotherapy with mitomycin C (MMC) and cisplatin (CDDP) in locally advanced squamous cell anal carcinoma with reference to radiotherapy (RT) combined with MMC and fluorouracil (5-FU).

Patients and methods: Patients with measurable disease >4 cm N0 or N+ received RT (36 Gy + 2 week gap + 23.4 Gy) with either MMC/CDDP or MMC/5-FU (MMC 10 mg/m^2 d1 of each sequence; 5-FU 200 mg/m^2/day c.i.v. daily; CDDP 25 mg/m^2 weekly). Forty patients/arm were needed to exclude a RECIST objective response rate (ORR), 8 weeks after treatment, of <75% (Fleming 1, $\alpha = 10\%$, $\beta = 10\%$).

Results: The ORR was 79.5% (31/39) (lower bound confidence interval [CI]: 68.8%) with MMC/5-FU versus 91.9% (34/ 37) (lower bound CI: 82.8%) with MMC/CDDP. In the MMC/5-FU group, two patients (5.1%) discontinued treatment due to toxicity versus 11 (29.7%) in the MMC/CDDP group. Nine grade 3 haematological events occurred with MMC/CDDP versus none with 5-FU/MMC. The rate of other toxicities did not differ. There was no toxic death.

☆ The current study was registered in ClinicalTrials.gov NCT00068744.

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Thirty-one patients in the MMC/5-FU arm (79.5%) and 18 in the MMC/CDDP arm (48.6%) were fully compliant with the protocol treatment ($p = 0.005$).

Conclusions: Radio-chemotherapy with MMC/CDDP seems promising as only MMC/CDDP demonstrated enough activity (RECIST ORR >75%) to be tested further in phase III trials; MMC/5-FU did not. MMC/CDDP also had an overall acceptable toxicity profile.

1. Introduction

Anal cancer is a rare disease accounting for approximately 2% of all gastrointestinal cancers.[1,2] However, its incidence has increased over the last 30 years in relation to infections with papillomavirus and with human immunodeficiency virus.[3–6]

Until the late 1960s, the mainstay of treatment was surgery, local resection and abdominoperineal resection for early and locally advanced disease respectively.[7,8] Pioneered by Papillon in France, radiotherapy alone achieved, in the early 1980s, results as good as surgery, whilst offering patients the chance to preserve the anal sphincter.[9]

In the early 1970s, improved results were observed with the combination of fluorouracil (5-FU) and mitomycin C (MMC) with radiotherapy.[10] Three randomised clinical trials definitively established that combining 5-FU and MMC with radiotherapy significantly increased local control and colostomy-free survival as compared with radiotherapy alone or with radiotherapy combined with fluorouracil for patients with locally advanced stages.[11–13]

In the two studies conducted in Europe, radiotherapy was given using a split-course scheme with a 6 week gap duration between the first sequence, delivering a 45 Gy dose over 5 weeks on a large volume, and a second sequence, delivering a 15–20 Gy boost-dose on the primary.[11,12] In the trial conducted in the US, the total dose was limited to 45–50 Gy over 5 weeks with field reduction at 30.6 and 36 Gy.[13] However, the locoregional recurrence rates remained as high as 30–40% in locally advanced tumours, indicating room for improvement. The European Organisation for Research and Treatment of Cancer (EORTC) 22953 phase II study tested the feasibility of an intensified treatment scheme reducing the gap duration to 2 weeks, delivering 5-FU and MMC during the two treatment sequences and using a protracted infusion of 5-FU over the whole treatment. As in the previous EORTC phase III trial, only patients with locally advanced disease were included. The compliance with the planned treatment was 93%; no grade 4–5 toxicity was observed. The complete response rate 6 weeks after treatment was 90.7%. As compared with the phase III trial, this modified scheme appeared to dramatically increase local control.

Meanwhile, cisplatin (CDDP) emerged as an active drug in the combined modality treatment (CMT) of anal carcinoma.[15–17] Since both MMC and CDDP seemed active components of CMT, the EORTC launched the present randomised phase II trial to confirm the feasibility of CMT with MMC and CDDP (MMC/CDDP) and to assess if it gives similar rates of early clinical response as the same radiation (RT) with MMC and continuous 5-FU (MMC/5-FU).

This trial was initially designed to continue as a randomised comparative phase III trial if both CMT's showed a minimum response rate of 75% in phase II.

2. Materials and methods

2.1. Eligibility criteria

Eligible patients had invasive squamous cell carcinoma of the anal canal; a WHO performance status of 0 or 1; were aged up to 75 years; had a granulocyte count above 2×10^9 cells/l; a platelet count above 100×10^9 cells/l; and a serum creatinine level less than 120 μmol/l. The extent of the tumours was evaluated by clinical examination, proctoscopy, computed tomography (CT) of the pelvis, ultrasonography (or CT scan with high dose contrast) of the liver and chest X-ray. Cytology for enlarged nodes was recommended. Tumours were staged according to the International Union Against Cancer (UICC) 1997 classification.[18] Only patients with measurable disease (RECIST definition[19]) were eligible: Patients with T2N0 equal to or greater than 4 cm in largest dimension, T3–4 N0 and N1N3, whatever the T classification, were included.

Patients with other histologies or who had been previously treated, or had other primary cancers, angina pectoris, distal arteritis or those who did not agree to use adequate contraception (who were at risk of pregnancy and breast feeding) were excluded. Written informed consent was required.

2.2. Treatment

Radio-chemotherapy was delivered in two sequences separated by a 2 week gap.

2.2.1. Radiotherapy

The treatment volume was defined in 3D on CT-based planning. The macroscopic primary tumour and involved lymph nodes were considered as the gross tumour volume (GTV).

2.2.1.1. First sequence. The clinical target volume of the first sequence (CTV1) included the GTVs and any sub-clinical disease including the perirectal nodes up to the top of the second sacral vertebra, the posterior pelvis, anteriorly a 3 cm margin beyond the macroscopical extension of the primary, laterally the internal iliac nodes and 3 cm of tissue beyond the primary, and downwards, the entire superficial anal perineum. The CTV1 was extended to the inguinal lymph node region when the primary was located 1 cm within the anal orifice or in case of pelvic lymph node involvement.

In case of inguinal lymph node involvement, the inguinal CTV1 included 3 cm of tissue surrounding the involved nodes. The planning target volume (PTV1) was defined by a 1 cm margin around the CTV1. The PTV1 was treated to a dose of 36 Gy delivered in 4 weeks (1.8 Gy/fraction, 5 fractions/week).

A treatment interruption of 2 weeks was planned between the first and second treatment sequences. The gap could be prolonged up to 5 weeks if the patient failed to fulfil criteria to resume treatment (acute toxicity ⩽ grade 2). Fig. 1 summarises the decision rules for starting the second treatment sequence.

2.2.1.2. Second sequence. The clinical target volume of the second sequence (CTV2) included all GTVs and a 1 cm margin. The planning target volume (PTV2) was defined by a 1 cm margin around the CTV2. Involved inguinal lymph nodes could be treated either by radio-chemotherapy alone (included in the CTV2) or by a surgical dissection after the completion of radio-chemotherapy and were therefore excluded from CTV2. The PTV2 was treated to a dose of 23.4 Gy delivered in 2.5 weeks (1.8 Gy/fraction, 5 fractions/week) by external beam radiotherapy or by interstitial brachytherapy (23.4 Gy specified at the 85% reference isodose).

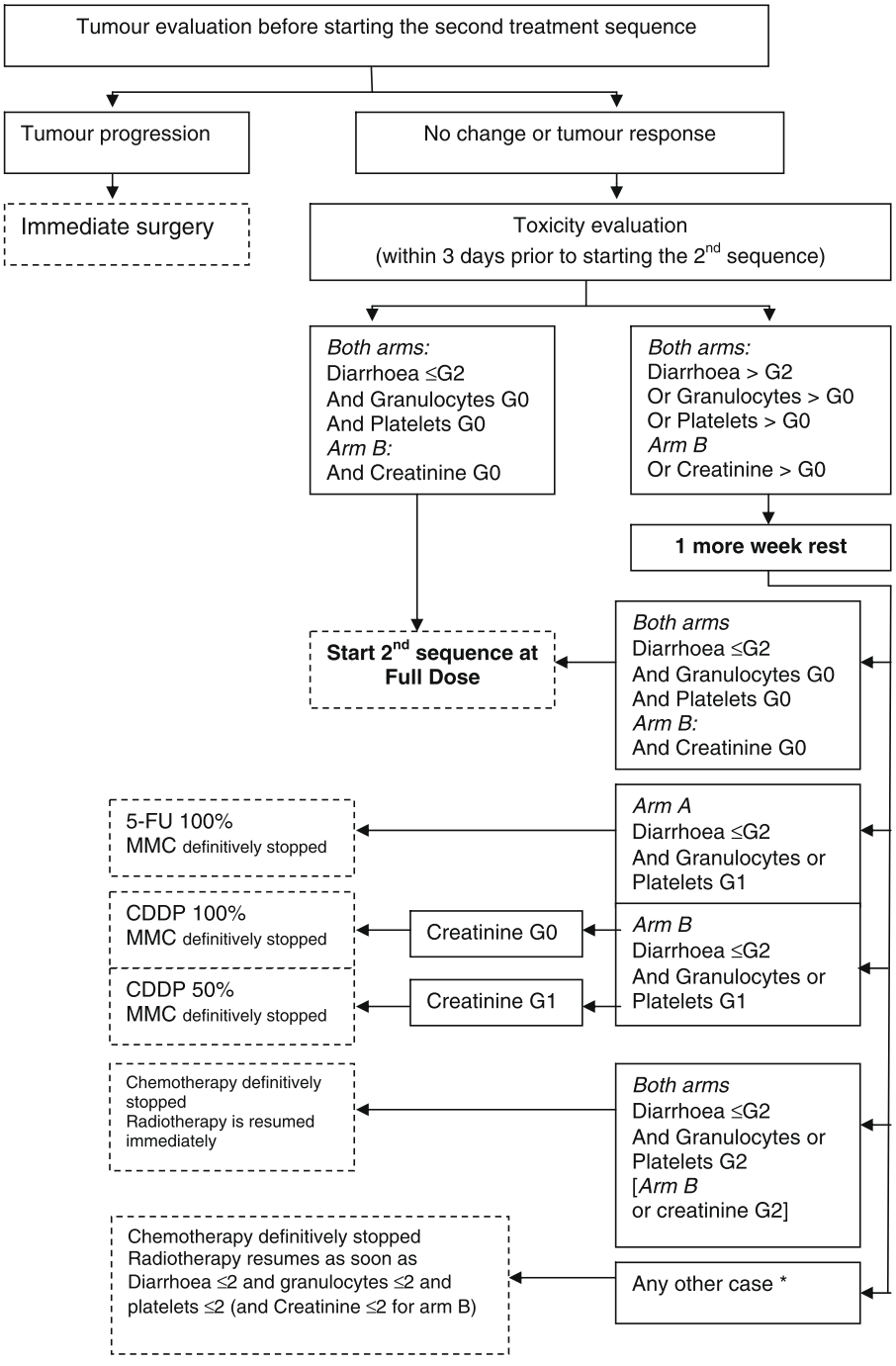


Fig. 1 – Decision scheme for second treatment sequence.

The doses to both PTVs had to be prescribed at the intersection of the beam axis and had to lie between 95% and 107% of the prescribed dose (ICRU 62[20]).

2.2.2. Concomitant chemotherapy

Chemotherapy started the first day of the first irradiation sequence. It was interrupted during the gap and re-initiated with the second irradiation sequence.

Patients of both arms received MMC 10 mg/m^2 before the first fraction of each irradiation sequence.

Patients in the MMC/5-FU arm received 5-FU 200 mg/m^2/day, in continuous infusion, from day 1 to 26 of sequence 1 and from day 1 to 17 of sequence 2. Patients in the MMC/CDDP arm received CDDP 25 mg/m^2, weekly, before the first radiotherapy fraction of each week during both sequences, $25 \times 7 = 175$ mg/m^2 total dose.

2.2.3. Surgery

If the tumour progressed before the second treatment sequence resumed, the patient was referred for surgery and the radio-chemotherapy was definitively stopped.

2.3. Follow-up

Patients were seen weekly during treatment, then every 2 weeks until 8 weeks after the end of treatment (week 16), then 10 weeks later (week 26), and then every 6 months. Visits included clinical examination with assessment of WHO performance status and toxicity scoring (CTCAE v3.0).[21] Local tumour and nodal response evaluation took place at week 6, and at week 16 (primary endpoint assessment), at week 26 and at every subsequent visit. Response of the primary tumour and inguinal nodes was assessed by clinical examination. Response of the pelvic nodes had to be assessed by CT scan. Whenever local recurrence was suspected, confirmation by biopsy was required.

2.4. Statistical considerations

The primary endpoint was tumour response (RECIST) 8 weeks after treatment (week 16). A 1-stage Fleming design[22] was applied independently to both randomised treatment groups with the aim of excluding a response rate $\leqslant$75% with a 1-sided type I error rate of 10%. In order to have 90% power to reject this hypothesis under the alternative that the true response rate was 90%, 40 patients were planned to enter each treatment group. Secondary endpoints were acute toxicity and satisfactory compliance to treatment that required all of the following: total irradiation dose $\geqslant$54 Gy, total treatment duration $\leqslant$67 days and% of total dose received $\geqslant$80% for all chemotherapeutic drugs. Confidence intervals were estimated by the exact binomial distribution for binary endpoints and by using the log-log transformation of the Kaplan–Meier estimates for time-to-event endpoints. Progression-free survival was counted from the day of randomisation to the day of first relapse or death of any cause. Event-free survival was counted from randomisation to relapse, death of any cause or colostomy, whichever occurred first.

3. Results

3.1. Patients

From November 2003 to May 2007, 88 patients were enrolled, of whom 10 were ineligible due to wrong TN classification and two because their disease was not measurable (Fig. 2, Consort diagram). The characteristics of the 76 eligible patients are reported in Table 1. The median follow-up for this analysis was 2 years (95% CI: 1.57–2.30).

3.2. Compliance to treatment

3.2.1. First treatment sequence

The median duration of the first CMT sequence was 26 days (range: 25–47 days) in the MMC/5-FU arm and 28 days (25–39 days) in the MMC/CDDP arm. The median radiotherapy dose was 36 Gy in both arms (34.2–40 Gy versus 34.2–36 Gy, respectively). Three patients in the MMC/5-FU arm stopped 5-FU injections because of haematological toxicity. In the MMC/CDDP arm, four patients stopped CDDP injections: two because of haematological toxicity and two because of diarrhoea grade 3. In the MMC/5-FU arm, the patients received MMC at a median dose of 100% of the full planned dose (range: 93.5–109.0%) and 5-FU at a median of 99.8% of the full planned dose (range: 53.9–119.7%). In the MMC/CDDP arm, the patients received MMC at a median dose of 98.9% of the full planned dose (range: 93.1–106.1%) and CDDP at a median dose of 99.8% of the full planned dose (23.8–106.1%). CDDP was stopped early in four patients due to haematological toxicity (two patients) or diarrhoea (two patients).

The median gap duration was 18 days (0–25 days) in the 5-FU/MMC arm and 19 days (2–32 days) in the MMC/CDDP arm. The gap was omitted in two patients in the MMC/5-FU arm and one in the MMC/CDDP arm. It was prolonged in 10 (25.6%) patients in the MMC/5-FU arm and in 17 (45.9%) in the MMC/CDDP arm. The reason for the gap being prolonged was toxicity in six patients in the MMC/5-FU arm (haematological toxicity in one and non-haematological toxicity in five) and in 13 patients in the MMC/CDDP arm (11 for haematological toxicity and two for non-haematological toxicities). The other reasons for prolonging the gap were holidays or patient convenience.

3.2.2. Second treatment sequence

The median duration of the second sequence was 17 days (3–28) and 17 days (9–36) in the MMC/5-FU and MMC/CDDP arms, respectively. The median radiotherapy dose was 23.4 Gy in both arms (21.6–24.4 Gy versus 9–24 Gy, respectively). Two patients in the 5-FU/MMC arm had their boost dose delivered by brachytherapy and received 23.4 Gy and 24 Gy to the 85% isodose, respectively. One patient in the MMC/5-FU arm refused the last radiotherapy fraction and one patient in the CDDP/MMC arm stopped after five fractions due to grade 3 neutropenia.

In compliance with the protocol, the second sequence was limited to irradiation only because of unresolved toxicity at the end of the treatment gap, in one and eight patients on the MMC/5-FU and MMC/CDDP arms, respectively.

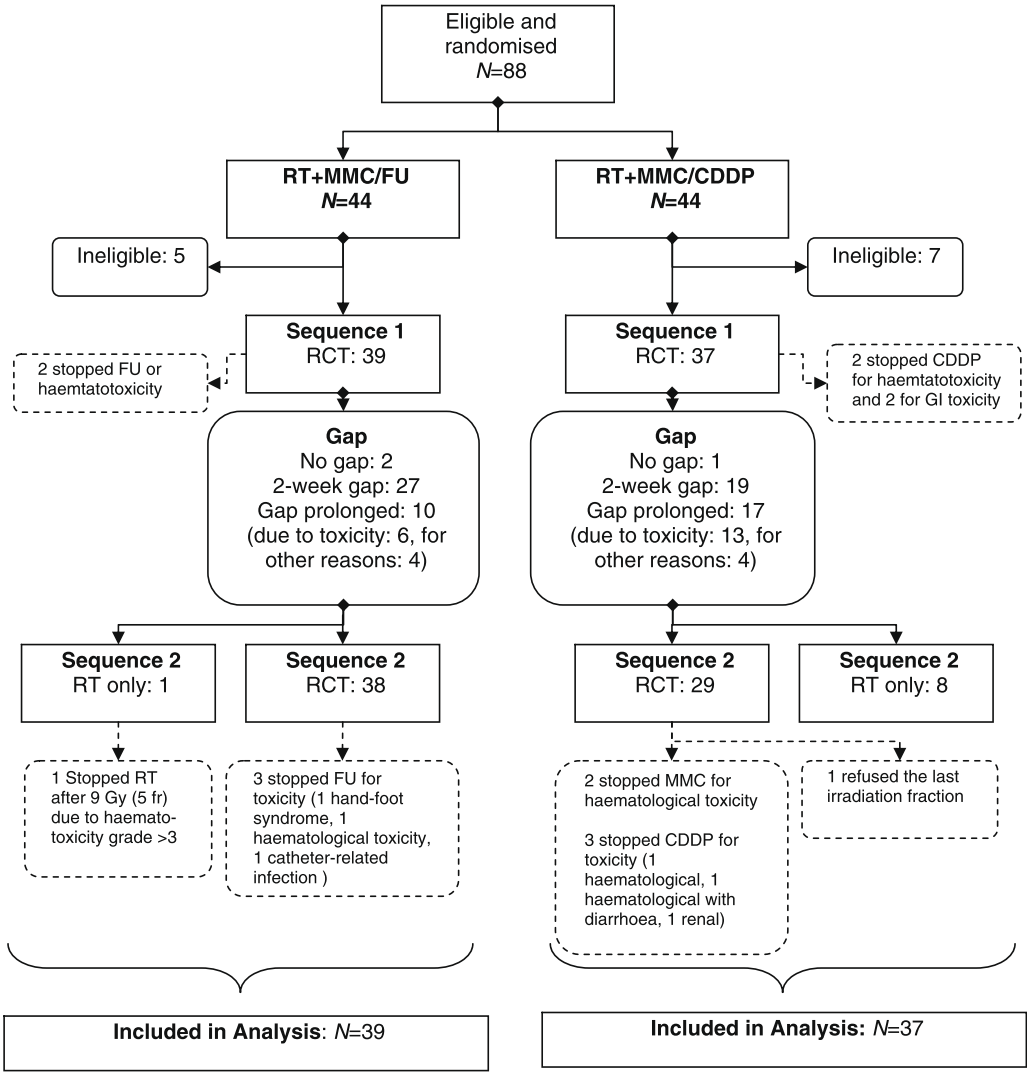


Fig. 2 – CONSORT diagram.

Patients in the MMC/5-FU arm received MMC at a median dose of 100% (range: 0–105.6%) and 5-FU at a median dose of 99.3% (0–139.5%) of the full planned doses of MMC and 5-FU, respectively. Those in the MMC/CDDP arm received MMC at a median dose of 99.5% (0–104.8%) and CDDP at a median dose of 97.1% (range: 0–106.0%) of the full planned doses of MMC and CDDP, respectively.

In the MMC/5-FU arm, three patients stopped 5-FU due to toxicity (hand-foot syndrome (1), haematological toxicity (1), catheter-related infection (1)). In the MMC/CDDP arm, two patients stopped MMC because of haematological toxicity and three stopped CDDP due to some other toxicity (renal (1), haematological (1), haematological and severe diarrhoea (1)).

In the MMC/5-FU arm, two patients (5.1%) discontinued all treatment because of acute toxicity versus 11 (29.7%) in the CDDP/MMC arm.

Overall, 31 patients in the MMC/5-FU arm (79.5%, 95% CI: 63.5–90.7%) and 18 patients in the MMC/CDDP arm (48.6%, 95% CI: 31.9–65.6%) fulfilled the three requirements for treatment compliance per protocol (Table 2, chi-square $p = 0.005$). These numbers are correct; in the first report, the patients who did not receive CT in the 2nd sequence were counted with a 0 dose for the calculation of their total RDI for the CT.

3.3. *Acute toxicity*

No toxic death was observed. Table 3 reports treatment related grade 3 and 4 acute toxicity: nine grade 3 haematological events were reported with CDDP/MMC versus none with 5-FU/MMC. The incidence of other toxicities did not differ between the treatment arms.

3.4. *Surgical procedures*

Surgical procedures related to severe treatment complications consisted of two total hip replacements due to late radiation toxicity in the MMC/CDDP arm and three colostomies for rectal complications (ulcer, severe pain, necrosis) (one in the CDDP/MMC arm and two in the 5-FU/MMC arm).

Table 1 – Patient/tumour characteristics.

	RT + 5-FU/MMC (N = 39)	RT + CDDP/MMC (N = 37)
Age (years)*		
Median	54.0	59.0
Range	37.0–73.0	39.0–75.0
Sex		
Male	14 (35.9)	9 (24.3)
Female	25 (64.1)	28 (75.7)
Performance status (WHO)		
0	33 (84.6)	28 (75.7)
1	6 (15.4)	9 (24.3)
Clinical T stage		
T1	1 (2.6)	0 (0.0)
T2	17 (43.6)	19 (51.4)
T3	16 (41.0)	13 (35.1)
T4	5 (12.8)	4 (10.8)
TX	0 (0.0)	1 (2.7)
Clinical N stage		
N0	20 (51.3)	19 (51.4)
N1	11 (28.2)	7 (18.9)
N2	5 (12.8)	8 (21.6)
N3	3 (7.7)	3 (8.1)
Max tumour diameter (mm)		
Median	50.0	50.0
Range	20.0–100.0	30.0–100.0

* p-Value for Wilcoxon test comparing age distribution: $p = 0.0272$; no significant difference for other factors.

Table 2 – Overall summary of treatment compliance.

	Treatment	
	RT + 5-FU/MMC (N = 39) N (%)	RT + CDDP/MMC (N = 37) N (%)
RT total dose ⩾54 Gy		
No	0 (0.0)	1 (2.7)
Yes	39 (100.0)	36 (97.3)
Total trt duration ⩽67 days		
No	3 (7.7)	5 (13.5)
Yes	36 (92.3)	32 (86.5)
Relative DI for all drugs ⩾80%		
No	6 (15.4)	17 (45.9)
Yes	33 (84.6)	20 (54.1)
Overall compliance to treatment		
No	8 (20.5)	19 (51.4)
Yes	31 (79.5)	18 (48.6)
95% Confidence interval*	63.5–90.7%	31.9–65.6%

* Chi-square $p = 0.005$.

3.5. *Tumour response 8 weeks after treatment*

In the 5-FU/MMC arm, 31 patients had an objective tumour response: 23 patients (59%) had a confirmed complete response (CR), eight had a confirmed partial response (PR) (20.5%) and one progressed. In the CDDP/MMC arm, 27 patients (73%) had a confirmed CR, seven had a confirmed PR (18.9%), three of them had a delayed CR, and none progressed (Table 4). Two patients in each treatment arm had a delayed CR response after a confirmed PR. One more patient in each arm was reported to have a CR during the follow-up but the measurements to confirm this statement were unavailable and thus these patients were classified as "unconfirmed CR". The overall response rates were 79.5% (lower bound of the CI: 68.8%) and 91.9% (lower bound of the CI: 82.8%) in the MMC-5-FU and MMC-CDDP arms, respectively.

Table 3 – Treatment related grade 3 and 4 toxicities.

	RT + 5-FU/MMC (N = 39) N (%)	RT + CDDP/MMC (N = 37) N (%)
WBC grade 3	0 (0.0)	8 (21.6)
Platelets grade 3	0 (0.0)	1 (2.7)
Nausea grade 3	1 (2.6)	5 (13.5)
Vomiting grade 3	1 (2.6)	1 (2.7)
Diarrhoea grade 3	5 (12.8)	2 (5.4)
Rectal bleeding grade 3	0 (0.0)	1 (2.7)
Inguinal dermatitis grade 3	2 (5.1)	4 (10.8)
Genital dermatitis grade 3	6 (15.4)	4 (10.8)
Perineal dermatitis grade 3	9 (23.1)	7 (18.9)
Mucositis grade 4	0 (0.0)	1 (2.7)
Proctitis grade 3	3 (7.7)	0 (0.0)

Table 4 – Tumour responses at week 16 (8 weeks after treatment).

	Treatment	
	RT + 5-FU/MMC (N = 39) N (%)	RT + CDDP/MMC (N = 37) N (%)
CR confirmed	23 (59.0)	27 (73.0)
CR unconfirmed	2 (5.1)	1 (2.7)
PR confirmed	8 (20.5)	7 (18.9)
PR unconfirmed	4 (10.3)	1 (2.7)
PD	1 (2.6)	0 (0.0)
Not assessable	1 (2.6)	1 (2.7)
Response to treatment		
No	8 (20.5)	3 (8.1)
Yes	31 (79.5)	34 (91.9)

3.6. *Survival*

With a median follow-up of 2 years, the median event-free, overall and progression-free survivals were not reached. The 1-year progression-free survival rate was 94.2% (95% CI: 78.5–98.5%) in the MMC/CDDP arm versus 76.3% (95% CI: 59.3–86.9%) in the MMC/5-FU arm (Fig. 3a). For the endpoint foreseen for phase III (event-free survival, Fig. 3b), the 1-year rates were 89.2% (95% CI: 73.7–95.8%) in the MMC/CDDP arm and 74.4% (95% CI: 57.6–85.3%) in the MMC/5-FU arm. In the MMC/5-FU arm, four patients died of their disease and one of chronic obstructive pulmonary disease caused by asbestosis. In the MMC/CDDP arm, one patient died of cardiovascular disease and one of haemorrhagic shock.

4. Discussion

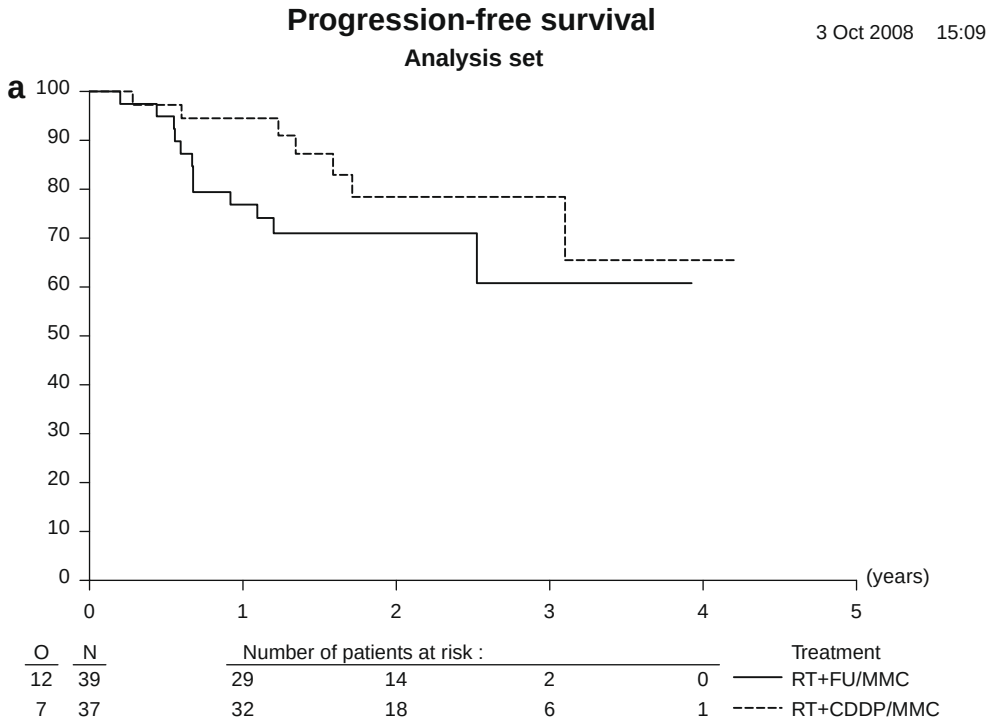
Chemoradiation is the standard treatment for locally advanced anal carcinoma.[11–13] EORTC 22953 demonstrated the safety of a treatment scheme with an interval gap reduced from 6 to 2 weeks, MMC delivered during both sequences and 5-FU delivered via continuous infusion during the entire treatment.[14] That treatment scheme seemed to improve local control and carry less late side effects compared to the previous EORTC study (EORTC 22861). Despite the lack of a randomised comparison, the EORTC adopted that scheme as the reference treatment (MMC/5-FU) and decided to compare it to a similar regimen where the chemotherapy with 5-FU and MMC was replaced by a combination of MMC and CDDP.

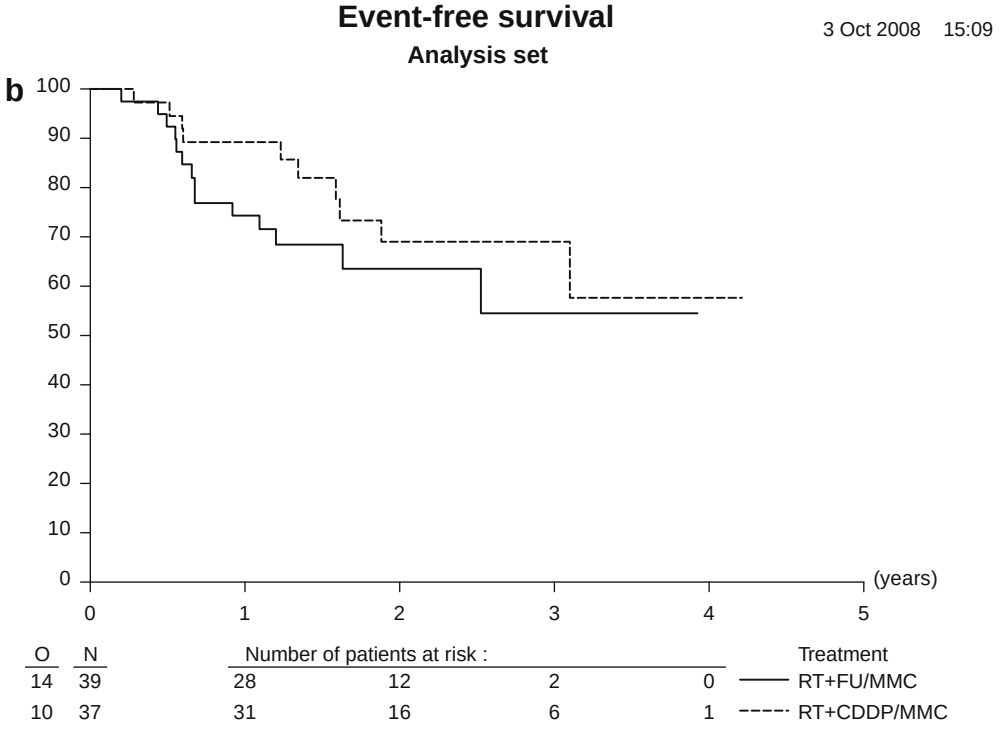
This study was initially planned as a randomised phase II/III trial assessing response rate in phase II and event-free survival in phase III. However, recruitment was suspended in May 2007 – phase II results being awaited before pursuing recruitment for phase III.

The statistical design required a minimum RECIST response rate of 75% in order to consider each treatment arm active. The results for the MMC/5-FU arm, however, remained compatible with a response rate lower than 75% (indeed, with 90% certainty, one could only exclude response rates below 68.8%). This treatment arm therefore failed the protocol conditions for testing in phase III. On the other hand, the response rate of the MMC/CDDP arm was 91.9%, showing with 90% confidence that the true response rate is at least 82.8%, satisfying the condition for phase III testing.

The 1-year progression-free survival rate of 94.2% (95% CI: 78.5–98.5%) observed with MMC/CDDP and of 76.3% (95% CI: 59.3–86.9%) observed with MMC/5-FU are in line with the response rate. For the endpoint foreseen for phase III (event-free survival) the 1-year rate was 89.2% (95% CI: 73.7–95.8%) with CDDP/MMC and 74.4% (95% CI: 57.6–85.3%) with 5-FU/MMC.

At the doses used in this study, the MMC/CDDP regime seemed to convey greater haematological toxicity than the





O = number of events, N = number of patients

Fig. 3 – (a) Progression-free survival. (b) Event-free survival in all eligible patients.

MMC/5-FU regime and had an overall compliance with treatment that was significantly lower (48.6% versus 79.5%).

The 8-week complete tumour response rates in the MMC-5-FU arm of this study appear far less than those observed in the 22953 study (53% versus 81%) despite the same treatment scheme and TN stage inclusion criteria.[14] However, the difference in the corresponding overall tumour response rates appears less significant (79.5% versus 90.7%). The measurement for each patient of both the T stage and the tumour's greatest dimension at inclusion (in strict adherence to

RECIST criteria) could explain this observed difference. Moreover, 10 patients with a tumour greatest dimension <4 cm, but extension into the rectum, were misleadingly classified as T3 and therefore were ineligible. This T stage misclassification may, however, have benefited previous studies. Another possible explanation of the CR difference is that MMC/CDDP is more rapidly effective. Nevertheless, all of the response rates, 1-year progression-free and 1-year event-free survivals indicate that MMC/CDDP has an early activity greater than that of the MMC-5-FU regime.

In view of a phase III trial, a pilot study adding CDDP to 5-FU/MMC with radiotherapy was conducted in UK. It resulted in unacceptable toxicity, especially haematological, and this scheme was abandoned.[23,24]

Other clinical researchers have attempted to replace either drug of the standard regime (5-FU/MMC), MMC by CDDP or 5-FU by capecitabine, and/or to test upfront chemotherapy.

Recently, the results of a large randomised phase III trial were reported that compared, in patients with $\geqslant$T2 N0 disease, the standard scheme of 5-FU/MMC to an experimental one including upfront chemotherapy with 5-FU/CDDP followed by CMT with 5-FU/CDDP. The experimental scheme failed to improve the disease-free survival and was associated with a significant increased rate of colostomy.[25] It was concluded that CMT with 5-FU/MMC should remain the standard of care. A phase II trial has evaluated the feasibility of CMT with capecitabine and MMC. Results suggest 5-FU may be replaced by capecitabine but it needs confirmation.[26] Developed 40 years ago, radiotherapy with concurrent 5-FU/MMC still remains the paradigm for locally advanced anal cancer; however, a CMT scheme with MMC-CDDP which has not been previously tested appears promising and we think this combination needs further development. We also think that targeted therapies need to take into consideration the biological profiles of these kinds of tumours. However, the selection of patients should be strictly limited to a population with very good conditions since our results suggest that a specific toxicity profile for such a combination could limit the compliance rate.

Conflict of interest statement

None declared.

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