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Editorial Comment

Anal cancer: One step forward – Two steps sideways!

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Someone, or nobody, knows I wot

Who or which or why or what

Is the Akond of Swat!

The final verse of Edward Lear's non-sense poem 'The Akond of Swat' could well describe our increasingly slippery grasp on how to improve the current treatment of anal cancer, which continues to elude us. Several recent trials have tantalisingly provided negative results[1–3] – although overall results appear to be improving.[2]

The results of the European Organisation for Research and Treatment of Cancer (EORTC) phase II study 22011-40014 are intriguing but also not constructively helpful for the future.

In squamous cell carcinoma of the anus, there are several potential strategies for improving loco-regional control: radiotherapy dose escalation, modifying field sizes, shortening or removing the gap, the addition of induction or consolidation chemotherapy before or after chemoradiation (CRT) and finally the integration of different chemotherapy agents into the CRT schedules.

The EORTC phase II study 22011-40014 opted to address the last of these questions, and in a small multicentre randomised phase II study compared 5-FU and mitomycin C (MMC) in combination with radiation versus MMC and cisplatin (CDDP) with radiation as definitive treatment of squamous cell anal carcinoma. The central role of MMC with 5-FU in anal cancer has been demonstrated.[4] However, many groups have also investigated the role of CDDP given in conjunction with 5-FU and radiotherapy.

The control arm in the EORTC 22011-40014 study represented the schedule from the previous EORTC 22953 phase II study, which used a schedule of CRT with a prolonged venous infusion of 5-FU coupled with MMC, but reduced the duration of the gap from the conventional 6–2 weeks.[5] 5-FU and MMC were both delivered during the two phases of radiotherapy. The published randomised trials[1,4,6,7] used a continuous 4- or 5-d infusion of 5-FU in the first and last weeks of radiotherapy. A prolonged venous infusion of 5-FU is an attractive alternative, with a more continuous radiosensitisation over the whole radiotherapy schedule.

The complete response rate in the EORTC 22953 study 6 weeks after the end of the treatment (14/15 weeks after the start of treatment) was 90.6%. The estimated 3-year local control rate was 88%, which compared with 68% in the former phase III EORTC 22861 trial.[6]

In the light of these results, the EORTC despite the lack of a randomised comparison designed a phase II/III trial (protocol 22011-40014) to compare what was considered an optimal 5-FU-MMC treatment with a similar but novel regimen where the chemotherapy with 5-FU and MMC is replaced by a combination of MMC and cisplatin (CDDP). The MMC/CDDP arm used a schedule of cisplatin more associated with cervix cancer – 25 mg/m^2 per week – giving a total of 25 mg/m^2 × 7 = 175 mg/m^2.

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The study uses a split course regimen to a dose of 36Gy in 20 fractions as the first sequence and after a 2 week gap (which could be prolonged to 5 weeks if acute toxicity had not settled), the second sequence delivered a further 23.4 Gy in 2.5 weeks (1.8 Gy per fraction) – i.e. a total dose of 59.4 Gy.

Eligibility was restricted to an advanced group with tumours T2 > 4 cm or node positive (N+). Upper age limit was 75 years. The primary endpoint was tumour response 8 weeks after the completion of treatment (i.e. week 16), with acute toxicity and compliance as secondary endpoints.

A total of 88 patients were enrolled (but 12 were ineligible – 2 because of non-measurable disease and 10 incorrect TN staging) giving 76 eligible patients. This high ineligibility rate probably reflects a study on a rare tumour by a co-operative group in centres which treat few patients, and should not simply be considered a measure of poor study quality.

Acute toxicity was similar except for 9 grade III haematological events in the MMC/CDDP arm compared with none in the control. In one and 8 patients, respectively, the second sequence delivered radiation alone because of haematological toxicity – but in general compliance to chemotherapy dose was excellent at >95%. The three components of compliance defined in the protocol as RT total dose >54 Gy, total treatment duration <67 d and relative dose intensity for all drugs >80% meant that only 47% of patients in the CDDP arm achieved overall compliance (confidence interval (CI) 31.9–65.6%).

Complete clinical response (RECIST) was confirmed at 8 weeks after treatment in 59% of patients on MMC/5-FU versus 73% on MMC/CDDP. It is not clear why the assessment time was shifted from 6 weeks in the two previous EORTC studies to 8 weeks in the present study. Cross study comparisons stray into statistical minefields and are invalid, and the small numbers make comparisons even more difficult. Yet, even if unconfirmed CR is added, the totals of 64% and 76%, respectively, achieving CR in the present study appear inferior to the results previously achieved in EORTC 22953, where the complete response rate 6 weeks after the end of the treatment (14/15 weeks after the start of treatment) was 90.6%. This difference is difficult to explain.

The gap was omitted in 3 patients but prolonged in 10 patients (25.6%) in the MMC/5-FU arm versus 17 (45.9%) prolonged in the MMC/CDDP arm – mainly because of haematological toxicity. So assessments presumably would be later (because of the prolonged gap) in the MMC/CDDP arm perhaps allowing more time for a response to be achieved.

With a median follow-up of 2 years, the 1 year progression free survival was 76.3% in the control versus 94.2% in the 5-FU/CDDP arm, and 1 year event free survival was 74.4% versus 89.2%, respectively.

What conclusions can we draw from this study? Complete clinical response is a good endpoint in anal cancer, and can be used in phase II studies to determine regimens to take forward into phase III studies. The level of tumour regression (>80%) after primary chemoradiation appears predictive of colostomy free and disease free survival.[8] The association of response with tumour T stage has been noted previously in anal carcinomas.[9,10] The Intergroup and EORTC trials[4,6] also reported a higher complete response rate on univariate analysis by tumour size.

Males usually fare worse than females[1] – hence a 12% excess of females in the CDDP arm may have contributed to the higher response rate although to some extent this might be offset by a slight excess of N2/N3 stage in the CDDP/MMC arm.

The randomised European trials advocated a 6 week gap in treatment following wide-field pelvic chemo-radiotherapy to a dose of 45 Gy prior to embarking on a more localised boost.[6,7] Several investigators have raised concerns about the negative impact of a treatment interruption in anal cancer or a long overall treatment time.[11,12] The gap may partly account for the results in the present EORTC 22011-40014 study for the control arm, and the fact that this regimen failed the protocol conditions to take into a phase III. These results contrast with ACT II, which abolished the gap completely, where CR at 18 weeks post CRT was 91% in both arms.[2] The most effective schedule would therefore seem to avoid any gap in radiation treatment.

So, where do we go from here? The initial study was intended to be extended to a larger phase III study if the efficacy rules were met. The authors highlight the good response rate in the MMC/CDDP arm, and suggest that the combination needs further development. However, they acknowledge that with limited compliance, this schedule might be difficult to take into a phase III setting. We appear to be able to integrate novel cytotoxic chemotherapy treatments only at the expense of excess acute toxicity and a consequent loss of compliance. The optimal chemotherapy regimen in combination with radiotherapy remains 5-FU and MMC without a gap. Other potential chemotherapy agents, such as vinorelbine, gemcitabine, paclitaxel, etoposide and topotecan have been investigated in cervix cancer both as single agents and in combination with cisplatin. Any of these might be investigated in anal cancer, and will need developing in future – along with novel biological agents. However, well-designed trials will need to enrol large numbers of patients, and any trial currently being developed will probably require international collaboration.

Conflict of interest statement

None declared.

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