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A clinical trial with protracted infusion 5-fluorouracil and mitomycin C for localised squamous cell carcinoma of the anus

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Running head: Protracted infusion FU and MMC for anal cancer

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ABSTRACT

Purpose

Mitomycin C (MMC) plus standard 5-fluorouracil (FU) infusion in weeks 1 and 5 often contributes to radiotherapy interruptions and possibly less-than-ideal outcomes in anal cancer. This study was to evaluate alternative strategies for chemotherapy delivery that might be less toxic or more efficacious, and outcomes of patient-initiated treatment interruption for severe acute toxicity.

Materials & Methods

This was a prospective, non-randomised study for patients with T1-4N0-3M0 anal squamous carcinoma. Radiotherapy of 54Gy in 30 fractions over six weeks was given with infusion FU 300mg/m^2/day for 96 hours/week for six weeks plus bolus MMC at 10mg/m^2 on D1.

Results

Fifty patients were recruited (72% female). Median age was 60.5 years (35-84). Forty-seven patients (94%) received 54Gy. Median duration of chemoradiation was 39 days (37-105). Grade 3 and 4 acute toxicity were observed in 66%. 31% with severe acute toxicity developed severe late toxicity. Of those who experienced severe late skin toxicity, 29% did not have severe acute toxicity.

Disease-free survival at 5 years was 74% (95% CI:60-84), and at 9 years 61% (95% CI:46-74). Overall survival at 5 years was 84% (95% CI:71-92), and at 9 years 67% (95% CI:50-81). Colostomy-free survival at 5 years was 70% (95% CI:56-81), and at 9 years 57% (95% CI:40-72).

Conclusion

It is feasible to deliver chemoradiation with bolus MMC and protracted infusion FU for anal cancer. Efficacy and toxicity of this regimen seem similar to conventional chemoradiation with FU/MMC. Acute skin toxicity is not a reliable predictor of severe late skin toxicity.

Key words

Anal cancer, chemoradiation, acute toxicity, late effects

INTRODUCTION

Chemoradiation has revolutionised the treatment of squamous cell carcinoma of the anus. It has evolved from a neoadjuvant role (1, 2) to becoming the definitive treatment. A series of landmark clinical trials that addressed various treatment factors, including: the issue of adding chemotherapy to radiation (3, 4), the specific role of mitomycin C (MMC) (5), the place for neoadjuvant and adjuvant chemotherapy (6, 7), the roles of MMC and cisplatin (6, 7), and selection of patients for elective inguinal radiation (8) have led to the current standard treatment of radiation with infusion 5-fluorouracil (FU) in weeks 1 and 5, and bolus dose MMC. This regimen provides superior tumour control, survival rates and functional outcomes. Improved radiotherapy technique with intensity-modulated radiation therapy (IMRT) has further refined an already excellent treatment with reduced acute toxicity (9).

Chemoradiation, however, often leads to significant acute perineal skin toxicity, and a treatment interruption is frequently necessary (7, 9-11). In a clinical trial evaluating radiation dose escalation, a planned treatment break of 2 weeks was incorporated into the treatment regimen with the

anticipation that a high percentage of patients would not be able to complete treatment uninterrupted. Unexpected suboptimal tumour control in this trial led to a reassessment of this strategy (12, 13).

Pelvic radiation combined with protracted infusion FU is the standard neoadjuvant preoperative treatment for locally advanced rectal cancer. It is generally well tolerated with low acute toxicity rates (14), and good compliance with few patients requiring treatment breaks. Our postulation was that delivery of FU with protracted infusion could reduce acute toxicity and potentially might minimise the rate of treatment breaks.

We conducted a single arm prospective study to investigate the efficacy of protracted infusion FU and MMC during the course of chemoradiation. In this study, standard chemotherapy with infusion FU given in weeks 1 and 5 was substituted with protracted infusion FU. We assessed tumour control, disease free rates, overall survival rates, colostomy-free survival rates, impact of treatment breaks, acute and late toxicity rates, and consequential effects of severe acute toxicity. We also assessed the outcomes of patient-initiated treatment interruption for severe acute toxicity.

MATERIALS AND METHODS

The study was prospective and non-randomised. Protocol approval was obtained from the ethics committee of the participating centre (Peter Mac HREC project No.: 97/58). Written informed consent was obtained from each participating patient.

Eligibility

Eligible patients were those with histologically confirmed squamous cell carcinoma of the anus, stage T1-4, N0-3, without evidence of metastatic disease, who had not undergone prior curative surgery for

the anal cancer. Performance status was required to be 0 or 1. Participants were required to have adequate bone marrow function with neutrophil count at least 1.5 x 10^9/L and platelet count at least 100 x 10^9/L, and adequate liver function, and serum creatinine less than twice the upper limit of normal. Patients with unstable cardiac disease, clinically significant active infection, concurrent active cancer in the last 5 years, or prior pelvic or abdominal radiotherapy were excluded. Patients had to be accessible for treatment and follow-up.

Treatment protocol

The treatment consisted of a single bolus dose of MMC followed by FU in continuous ambulatory infusion administered with a radical course of pelvic radiotherapy.

MMC was dosed at 10mg/m^2 and administered as a bolus dose on the first day of radiotherapy. The FU was administered at 300mg/m^2/day via ambulatory infusion pump for 96 hours a week for the whole course of radiotherapy, beginning on the first day of radiotherapy and stopping immediately after the last radiotherapy treatment.

All gross disease, both anal and involved nodes, was treated to a total dose of 54Gy, 1.8Gy/fraction, 5 days per week, over 6 weeks. Prophylactic radiotherapy of 36Gy was given to the inguinal regions for T2-T4 and for patients with involved nodes.

Radiotherapy was delivered in 3 phases: pelvic-inguinal field, pelvic field, and boost field. Pelvic fields were planned to cover the primary tumour and lateral pelvic nodes. The superior border was at the inferior sacroiliac joints, or 5cm proximal to the primary tumour, whichever was more

proximal. The inferior border was 3cm below the primary tumour. The lateral borders were 1cm lateral to the pelvic brim. The posterior border was a minimum of 1cm behind the anterior bony sacral margin, and the anterior border was 3cm anterior to the primary tumour. The boost field was planned to treat the tumour and clinically involved nodes with a 2cm margin.

For T1 N0 M0, the pelvic field was treated to 45Gy in 25 fractions, in 1.8Gy per fraction over a 5-week period, with a 3-field technique. This was followed immediately by the boost field for another 9Gy in 5 fractions over 5 days. No attempts were made to cover the inguinal regions. For T2-4 N0-1 M0, the pelvic-inguinal field was treated to 36Gy in 20 fractions, in 1.8Gy per fraction over 4 weeks, with anterior and posterior opposing fields. The pelvic field received an additional 9Gy. A further 9Gy was delivered to the boost field. In total, gross tumour was treated to a dose of 54Gy and inguinal regions a dose of 36Gy. For T1-4 N2-3 M0, the radiotherapy field and dose were identical to that for T2-4 N0-1 M0 except the involved inguinal region was treated with electron field to a total dose of 54Gy. The uninvolved inguinal region was treated to 36Gy only.

Treatment interruption

Radiotherapy interruption was allowed after grade 3 or grade 4 toxicity. Radiotherapy was recommenced once toxicity grade had decreased to 2 or lower. Chemotherapy was interrupted in the event of any radiotherapy interruption, and recommenced once radiotherapy resumed.

Chemotherapy was interrupted for grade 3-4 non-haematological toxicity that was clearly due to chemotherapy alone and resumed with a dose reduction at the discretion of the investigators. FU infusion was ceased if grade 3 or 4 neutropaenia or thrombocytopaenia developed, or if severe

neutropaenia or thrombocytopaenia was expected to develop. Plantar-palmar syndrome induced by FU was managed according to severity. Patients with mild to moderate symptoms of dryness and erythema with pain had continued FU infusions, with pyridoxine 50mg orally three times daily prescribed throughout treatment. Severe plantar-palmar syndrome characterised by blistering and desquamation was managed with pyridoxine, and interruption of FU infusion for at least one week.

Patient assessments

Pre-treatment assessments included clinical evaluation (history, physical examination, WHO performance status assessment, and toxicity assessment), full blood examination (FBE), renal and liver function tests, tumour biopsy, chest X-ray and CT abdomen and pelvis.

Assessments during treatment included weekly FBE blood tests and toxicity assessments. At 2 weeks after completion of chemoradiation, FBE, renal and liver function tests were taken, and toxicity and performance status were assessed. The patient was assessed for clinical response at 2 months after completion of treatment, and 2 monthly until complete response was observed. Thereafter, the patient was assessed every 3 months for toxicity and disease status.

Statistical considerations

The accrual target of this study was 50 patients. Accrual was expected to be completed in 60 months. With this sample size, the overall response rate (complete and partial responses) would be estimated with a maximum standard error of 7%.

Patient demographics, pre-treatment disease characteristics and treatment received were summarised using descriptive statistics, including the median and range for data measured on a continuous scale and counts and percentages for categorical data. Percentages were rounded up to the nearest whole number.

Acute and late radiation morbidity were assessed according to the appropriate EORTC/RTOG scoring criteria (15). All toxicities were summarised by grade and grade 3 or 4 toxicities were specifically listed together with time of onset (from start of protocol treatment).

The objective response rate was calculated as the number of complete or partial responders divided by the number of patients who commenced treatment, expressed as a percentage. The 95% confidence interval for the objective response rate was calculated using the Blyth-Still-Casella method.

The treatment interruption rate was calculated as the number of patients having a RT treatment interruption due to toxicity as a percentage of all patients who commenced treatment. The 95% confidence interval for the interruption rate was calculated using the Blyth-Still-Casella method.

Disease-free survival was measured from the date of commencement of RT until the date of first failure, where failure was persistent disease or recurrence, or death from any cause. For patients with persistent disease, disease-free survival was measured from the commencement to conclusion of RT. Colostomy-free survival was measured from the date of commencement of RT until the date of colostomy or death, whichever occurred first. Overall survival was measured from the date of commencement of RT until the date of death from any cause.

The Kaplan-Meier method was used to estimate disease-free survival, colostomy-free survival and overall survival for all patients. Times were censored at the study close-out date for patients who were still being followed up without having experienced the relevant event by the close-out date, or the date of last contact for patients lost to follow-up without a prior event. For disease-free survival, the location of first failure was summarised and a competing risks analysis was used to estimate cumulative incidence rates for each type of failure.

Quality control

Data were collected on study specific case record forms designed by the study statistician. The study co-ordinator entered the data into a database created by the trial centre, using Microsoft Access software. Data queries were generated by the study co-ordinator in liaison with the study statistician. All queries were rectified at the time the statistical report was completed.

RESULTS

Fifty patients were recruited between December 1997 and May 2003. Of these, 36 were female (72%). The median patient age at time of registration was 60.5 years, and the range of ages of the participants was 35 to 84. The patient characteristics are listed in Table 1.

Protocol compliance

Forty-seven patients (94%) received 54Gy to the tumour. Prophylactic inguinal nodal irradiation was delivered to 33 patients (66%). Fifteen patients with involved inguinal nodes were treated to the tumour dose (54Gy in 87%). 7 patients (14%) had reductions in FU dose. 8 (16%) had breaks in FU infusion while continuing radiotherapy. The median duration of chemoradiation was 39 days (37-105 days).

Thirteen patients (26%) had a break in the delivery of their planned chemoradiation: 12 due to severe toxicity, and 1 due to treatment overlapping public holidays. Of those with treatment breaks due to toxicity, 10 breaks were due to grade 3 or 4 perineal skin toxicity, 1 was due to hospitalisation for investigation of fever and diarrhoea, and 1 was for nausea, diarrhoea and abdominal pain.

Treatment-related toxicity

Acute radiation toxicities are listed in Table 2. Pelvic skin and lower GI toxicities were most common. Pelvic skin toxicity was the commonest severe acute toxicity experienced (G3 62%, G4 2%). Lower GI tract toxicities were mainly grade 1 and 2 (G1 21%, G2 48%, G3 4%).

Late radiation toxicities are listed in Table 3. All patients had differing degrees of skin changes. Gastrointestinal toxicity was also common, with most cases being grade 1 (62%) or 2 (16%). No cases of grade 3 or 4 toxicity were noted.

In correlating between acute and late toxicity, a total of 32 patients developed Grade 3 or higher acute skin toxicity. Of those, 10 patients developed G3 or higher late skin toxicity (31%). Conversely, in 14

patients who developed G3 or higher late skin toxicity, 4 patients (29%) did not experience severe acute skin toxicity. 10 patients had treatment interruptions due to severe acute skin toxicity. Half of these (5 patients) subsequently developed G3 or 4 late skin toxicity.

Survivals and failures

The median potential follow-up was estimated at 7.3 years.

The estimated disease-free survival rate at 5 years was 74% (95% CI 60% - 84%) and at 9 years was 61% (95% CI 46% - 74%). See Figure 1.

The estimated overall survival rate at 5 years was 84% (95% CI 71% - 92%) and at 9 years was 67% (95% CI 50% - 81%). See Figure 2.

Cumulative incidence by location of first failure at 5 years and 9 years were 16% (S.E. 5%) and 18% (S.E. 6%) for local failure, and 4% (S.E. 3%) and 4% (S.E. 3%) for distant failure respectively. Of 8 patients who failed locally, 2 patients (25%) had treatment breaks.

Eight patients (16%) were known to have had a colostomy, with a further eleven patients dying without having received a colostomy. The estimated colostomy-free survival rate at 5 years was 70% (95% CI 56% - 81%) and at 9 years was 57% (95% CI 40% - 72%).

DISCUSSION

In this study, chemoradiation with protracted infusion FU and bolus dose MMC had similar tumour control and survival rates compared to randomised studies. The 5-year disease-free survival of 74% (95% CI 60% - 84%) compared favourably with RTOG 98-11 (67.8%), and ACT II (69%). The estimated overall survival rate at 5 years of 84% (95% CI 71% - 92%) was comparable to RTOG 98-11 (78.3%) and ACT II (79%). The colostomy-free survival rate was also comparable: 70% (95% CI 56% - 81%) at 5 years compared to 72% for RTOG 98-11, and 75% at 3 years for ACT II (6, 7, 16).

We did not observe reduction of severe perineal skin toxicity with this regimen. Grade 3-4 toxicity rates were similar to other studies where high dose infusion FU was given in week 1 and 5 together with MMC. In the RTOG 98-11 trial, grade 3-4 toxicity occurred in 58.8%, with skin toxicity the most common event. In the ACT II trial, grade 3-4 toxicity occurred in 48% of patients in the FU/MMC group during chemoradiation.

Although protracted infusion does not seem to be superior to conventional FU/MMC chemoradiation both in terms of efficacy and toxicity, it remains an attractive proposition in clinical practice. The whole treatment can be delivered as an outpatient procedure, and it eliminates the risk associated with high dose FU infusion.

Although severe skin toxicity leading to treatment interruption is common, a clear guide to the best time for a treatment break is lacking. Patient tolerance to toxicity symptoms varies. Completion of treatment without treatment break in the presence of grade 3 skin toxicity is not unusual.

Prescribing a treatment interruption for early signs of grade 3 toxicity may be unnecessary and may compromise tumour control. Conversely, delaying a treatment interruption may put the patient at risk of increased late complications as a result of consequential effect.

At our institution, we have an established policy to minimise treatment interruption due to concerns of negative impacts on tumour control. More emphasis is placed on patient-reported symptoms than physician observations when considering treatment interruptions for skin toxicity. Patients attend an education session at the beginning of the treatment course, where educators emphasise the importance of timely completion of treatment, and encourage patients to complete the entire treatment course without interruptions. Severe grade 3 toxicities are not uncommon at the time of treatment break. While the policy avoids breaks for skin reactions that the patient can manage, it may run the risk of increasing late skin toxicity. This trial also provides an opportunity to assess this policy in a prospective clinical trial setting. Meticulous follow up allowed accurate assessment of acute and late toxicities for each individual patient.

We reviewed individual data and correlated grade ≥ 3 acute and late skin toxicity. 31% of patients with severe acute toxicity developed severe late toxicity. Of those who had severe late skin toxicity, 29% did not have severe acute toxicity. In addition, toxicity-related treatment breaks did not eliminate severe late toxicity, as 50% of this group subsequently developed late toxicity. Our data suggest that acute skin toxicity is not a reliable predictor for severe late skin toxicity.

IMRT was not used in this study. All patients were treated with 3D conformal radiotherapy. Improvement of radiotherapy techniques with IMRT will enable delivery of radiation to a highly conformal target volume. Minimising radiation dose to the small intestine will reduce

gastrointestinal toxicity (17). Reducing the dose to bone marrow will decrease haematotoxicity. Optimising dose homogeneity will further reduce toxicity and improve tumour control. However, as the primary anal cancer will always require high dose radiation of 50Gy or more, it will be difficult to substantially reduce skin toxicity even with these highly conformal techniques. The policy of interruption according to patient-reported toxicity will be a useful guide for timing treatment breaks.

The backbone of chemoradiation for anal cancer has not changed for many years. 50-55Gy in combination with chemotherapy is the standard treatment for nearly all patients. While this is an effective treatment with a high success rate, this one-size-fits-all approach clearly needs to be refined. The ongoing PLATO (Personalising anal cancer radiotherapy dose) comprises 3 separate trials which aim to optimise radiotherapy dose for low-, intermediate- and high-risk anal cancer (18). This trial may provide guidance to the optimal radiation dose for different stages of disease.

It is also possible that radiation doses can be adjusted according to other risk factors, such as p16 status. Carcinomas of the anal canal are strongly associated with human papillomavirus (HPV). Expression of p16 is used as a surrogate marker of HPV infection, and p16 positivity is an independent prognostic factor for overall survival and disease free survival (19). It also appears to be an important factor in local control (20). Other opportunities for de-escalation of radiation dose exist (21). Further study is needed to improve an already excellent treatment.

Although randomised data are not available to support its use, capecitabine has been widely accepted in chemoradiation for anal cancer. It is welcomed by consumers for its convenience, and by health authorities for its lower treatment cost. It is comforting to learn that two large-scale retrospective studies have shown its safety and efficacy (22, 23). The current PLATO randomised

study will provide data to confirm this observation. As it is likely that future improvement will come in small increments, the importance of conducting randomised trials for this rare cancer cannot be overstated.

The strength of this study is that it is a prospective study, and all patients were treated in a single institute by the lower gastrointestinal radiation oncology team. The compliance rates in terms of registration of patients, treatment delivery, and data collection were high. No patients were lost to follow up. Prospective collection of acute and late toxicity allowed acute and late toxicity analysis for each patient. Although the study sample was relatively small, a high acute perineal skin toxicity rate allowed credible assessment of possible consequential effect, as well as assessment of treatment breaks initiated by patient-reported toxicity.

As far as we are aware, correlation of acute with late reactions in individual cases has not been reported in anal cancer. However, the small sample size would not allow assessment of the relative efficacy and safety of this regimen compared to the traditional approach of chemoradiation with bolus MMC and week 1 and 5 infusion FU. Our regimen does not seem to be inferior to this standard, but confirmation is necessary.

CONCLUSION

It is feasible to deliver chemoradiation with bolus MMC and protracted infusion FU for anal cancer. Efficacy and toxicity of this regimen seem similar to conventional chemoradiation with FU/MMC. Acute skin toxicity is not a reliable predictor for severe late skin toxicity.

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Figure Legends:

Figure 1

Disease free survival

Kaplan-Meier curve of disease-free survival from date of commencement of radiotherapy. Ninety-five percent confidence intervals are shown by dotted lines. Patients with censored times are shown by tick marks.

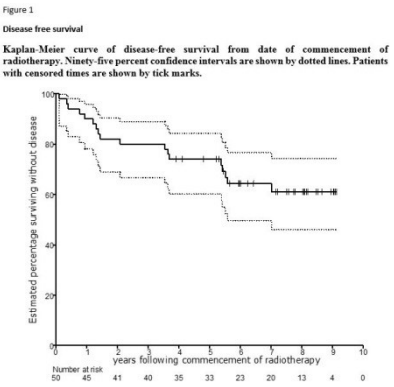

Figure 2

Overall survival

Kaplan-Meier curve of overall survival from date of commencement of radiotherapy. Ninety-five percent confidence intervals are shown by dotted lines. Patients with censored times are shown by tick marks.

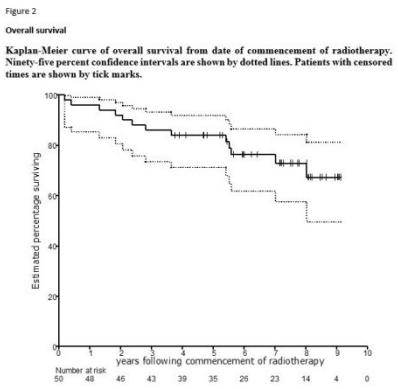

Table 1

Patient Characteristics

Characteristic	*Category*	*Statistic*	
		No. Patients	*Percentage Patients*
Histological grade at initial diagnosis	Well differentiated	5	10%
	Moderately differentiated	19	38%
	Poorly differentiated or undifferentiated	17	35%
	Mixed differentiation[1]	2	4%
	Not specified	7	14%
Staging method	Clinical examination	50	100%
	CT scan of abdomen & pelvis	49	98%
	Endo-rectal ultrasound	16	32%
	Chest x-ray	35	70%
	Other[3]	16	32%
T stage	1	11	22%
	2	20	40%
	3	6	12%
	4	13	26%
N stage	0	33	66%
	1	2	4%
	2	7	14%

	3	8	16%
M stage[4]	0	50	100%
Stage Grouping[4]	1	10	20%
	2	17	34%
	3a	7	14%
	3b	16	32%
WHO performance status	0	29	58%
	1	21	42%

Table 2

Acute radiotherapy toxicities

		Statistic	
		No.	***Percentage***
Toxicity	***Worst Grade***	***Patients***	***Patients***
Skin (pelvic)	0	0	0%
	1	3	6%
	2	15	30%
	3	31	62%
	4	1	2%
Lower GI tract, including pelvis	0	3	6%
	1	21	42%
	2	24	48%
	3	2	4%
	4	0	0%
Genitourinary	0	16	32%
	1	24	48%
	2	9	18%
	3	1	2%
	4	0	0%
Stomatitis/mucositis	0	35	70%
	1	10	20%
	2	4	8%

	3	1	2%
	4	0	0%
Nausea	0	21	42%
	1	21	42%
	2	8	16%
	3	0	0%
	4	0	0%
Vomiting	0	41	82%
	1	8	16%
	2	1	2%
	3	0	0%
	4	0	0%
Skin (hands, feet)	0	48	96%
	1	2	4%
	2	0	0%
	3	0	0%
	4	0	0%

Table 3

Late radiotherapy toxicities

		Statistic	
Toxicity	***Grade***	***No. Patients***	***Percentage Patients***
Skin (pelvic)	0	0	0%
	1	12	24%
	2	22	44%
	3	13	26%
	4	1	2%
	Not assessed	2	4%
Subcutaneous tissue	0	1	2%
	1	23	46%
	2	18	36%
	3	6	12%
	4	0	0%
	Not assessed	2	4%
Small/large intestine	0	9	18%
	1	31	62%
	2	8	16%
	3	0	0%
	4	0	0%
	Not assessed	2	4%
Bladder	0	33	66%
	1	8	16%
	2	5	10%
	3	2	4%
	4	0	0%
	Not assessed	2	4%