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PHASE II STUDIES

Phase II study of mitomycin-C, adriamycin, cisplatin (MAP) and Bleomycin-CCNU in patients with advanced cancer of the anal canal: An eastern cooperative oncology group study E7282

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Summary Metastatic anal cancer is a rare disease in the Western hemisphere and current treatment modalities are not effective. In this study, patients with advanced epithelial cancer of the anal canal received MAP followed by Bleomycin and CCNU upon progression of disease. Twelve out of twenty eligible patients had a partial response 60%, (95% CI {36% −81%}). No complete responses were observed. The median survival was 15 months (95% CI {6–20} months). The median time to progression or death was 8 months (95% CI {4–9 months}). Toxicities were moderate and tolerable with routine supportive care; there were 2 cases of grade 3 vomiting, 2 cases of respiratory distress (one grade 1 and one grade 3), one case each of grade 3 leg cramps and cardiac arrhythmia. Of particular note were 7 cases of grade 3 hematologic toxicity. Two patients had grade 4 leukopenia and thrombocytopenia, respectively, that resolved without sequelae. The combination therapy of MAP followed by Bleomycin and CCNU for patients with advanced anal cancer, not amenable to radiotherapy or surgery, results in a moderate objective response but with moderate toxicities. This regimen and sequence is worthy of further study especially in combination with colony stimulating factors, however, its tolerability may be most applicable for patients who have had minimal prior therapy.

Keywords Anal cancer · Mitomycin-C · Adriamycin · Cisplatin · Bleomycin · CCNU · Phase II

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Introduction

Epidermoid anal cancer is a rare malignancy and accounts for approximately 2% of all large bowel malignancies. It tends to be a locally invasive malignancy with only 50% of cases surviving for 5 years after radical or local excision [1, 2]. High dose external beam radiotherapy alone gives survival rates of up to 75% at 3 years and interstitial irradiation produces local control rates of up to 50% [3]. This has translated into two-thirds of patients surviving for 5 years while maintaining adequate sphincter function. Norman Nigro and collegues pioneered combined modality chemoradiotherapy (CMT) in order to convert inoperable cases into candidates for surgical salvage [4]. In a landmark trial, the UK Co-ordinating Committee on Cancer Research (UKCCCR) was set up to compare the most promising regimens of radiotherapy alone versus CMT. The trial demonstrated that standard treatment

for most patients with anal cancer should be a combination of radiotherapy with infusional 5-Fluorouracil (5-FU) and Mitomycin-C, and surgery reserved for those who fail this regimen [5]. Despite the success with this regimen, there is still a 40–50% failure rate and patients eventually requiring surgical salvage and /or subsequent chemotherapy [6, 7]. To-date, 5-FU, Bleomycin, Adriamycin, Mitomycin-C, CCNU, Methyl-CCNU, and cis-platinum have been identified as having activity in anal cancer [6–9]. Mayo Clinic (Rochester, MN) has piloted the efficacy of sequential Bleomycin and CCNU in patients with advanced anal carcinoma. In their limited unpublished experience, three of 7 patients treated with this regimen have had significant and prolonged partial remission of metastatic disease. The toxicities of this regimen were moderate and included nausea and vomiting that was controlled by standard anti-emetic regimens. Moderate degree of stomatitis was seen in these patients, however this subsided by the next treatment cycle. Of 37 patients with a variety of malignancies having received this treatment (pancreatic—3 pts; esophageal—16 pts; colorectal cancer—14 pts), moderate nausea/vomiting was seen in 19 patients and stomatitis in 11 patients. In another report using this regimen for the treatment of squamous cell carcinomas, 3 of 6 patients treated with Bleomycin alone or in combination with CCNU had a partial response. Mayo Clinic also piloted a combination regimen of Mitomycin-C, Adriamycin and cis-platinum (MAP) in 63 patients with extensive non-small cell lung cancer. Toxicities were moderate with myelosuppression being a common toxicity (34% of these patients had WBC nadirs $<2500\ /\mu$L. 30% of patients had platelet count nadirs $<75{,}000\ /\mu$l) at some point during the course of their therapy. Nausea/vomiting was more severe and was seen in 70% of patients. Other significant and frequent side-effects included alopecia and skin rash. In combining the two experiences, namely MAP followed by sequential Bleomycin and CCNU, in April 1983, the Eastern Cooperative Oncology Group (ECOG) embarked upon a phase II trial to define the efficacy of such sequential treatment in patients with advanced anal carcinoma. The purpose of this trial was to investigate the effectiveness and tolerability of the combination regimen of MAP in patients with metastatic anal canal cancer, and to determine the anti-tumor activity of the combination of Bleomycin and CCNU as subsequent line treatment in patients with anal cancer who have failed primary MAP therapy.

Methods

Eligible patients with ECOG performance score ≤ 3 were required to have histologically documented metastatic, locally recurrent or residual carcinoma of the anal canal (excluding perianal and non-epithelial tumors) with unidimensionally measurable disease. For the purposes of this study, measurable disease entailed disease clearly measurable with a caliper or ruler; hepatomegaly (provided there was histologically proven liver metastasis), if clearly palpable, the liver edge extended at least 5 cm below the xiphoid process or the costal margins on quiet respiration or Computerized Tomography (CT) scan or radioactive tracer scan measurements demonstrated it was at least 5 cm in greatest diameter. Patients were not allowed on this study if they had received prior Adriamycin, cis-platinum, Mitomycin-C or Bleomycin; however during the conduct of this study eligibility was changed such that patients were allowed if they had received prior Mitomycin-C of no more than 2 cycles of treatment. Patients should not have had major surgical procedures or anastomosis or chemotherapy within 4 weeks of registration. Prior to study entry, patients should not have had a concomitant malignancy and should have an estimated food intake of ≥ 20 cal/Kg/day without the need for parenteral alimentation. Patients were required to have adequate organ function which included serum creatinine ≤ 1.5 mg/dL for patients initially entered on the Bleomycin and CCNU arm. Subsequently, study amendment further required serum creatinine ≤ 1.5 mg/dL for patients receiving MAP. Other organ function parameters for all patients included platelet count $\geq 130{,}000\ /\mu$L and leukocyte count $\geq 4000\ /\mu$L. The study was approved by the Investigational Review Boards of the participating institutions and all the patients gave informed consent.

Eligible patients were classified by histologic type as basaloid, squamous, basaloid small cell carcinoma and by tumor cell grade as well, moderately and poorly differentiated at registration, however, specific accrual goals were not sought within these patient subsets. All eligible patients after registration received Mitomycin-C at 10 mg/m^2 intravenously over 5–10 min on day 1 followed by Adriamycin at 30 mg/m^2 intravenously over 5–10 min on day 1 and cis-platinum 60 mg/m^2 intravenously in 1000 ml D5-0.5%NS over 2 hr on day 1. Each drug was repeatedly administered every 4 weeks (one cycle) for 2 cycles. Following the completion of 2 cycles of MAP, Mitomycin-C was administered every 10 weeks, Adriamycin and cis-platinum was administered every 5 weeks. Prior to each dose of cis-platinum, 25 gm of mannitol was diluted in 1000 ml cis-platinum solution and 40 mg of furosemide (Lasix®) was administered orally 30 min prior to initiation of treatment. Those patients who developed progressive disease while on MAP, if still eligible were then treated with the second study step therapy of sequential Bleomycin- and CCNU. Bleomycin was administered at a dose of 25 mg/m^2 in D5W intravenously daily until a total cumulative dose of 280 mg or toxicity. CCNU was administered at a dose of 130 mg/m^2 orally on day 1, and then repeated 4 weeks after completion of Bleomycin, this was repeated every 6 weeks. Within 4 months of the

start of this study, the daily dose of Bleomycin was reduced from 25 mg/m^2 to 10 mg/m^2; however, the cumulative dose remained the same. Bleomycin was discontinued if any pulmonary toxicity was observed.

Dose reductions of each drug were performed for the worst toxicity observed. The dose of CCNU and Mitomycin-C for subsequent cycles were reduced by 33, and 50% for granulocytes $\geq 1.0 - < 2.0 \times 10^9$/L and/or platelets $\geq 25 - < 75 \times 10^9$/L and granulocytes $< 1.0 \times 10^9$/L and/or platelets $< 25 \times 10^9$/L, respectively. The dose of Adriamycin for subsequent cycles was reduced by 25% and 33% for granulocytes $\geq 1.0 - < 2.0 \times 10^9$/L and/or platelets $\geq 25 - < 75 \times 10^9$/L and granulocytes $< 1.0 \times 10^9$/L and/or platelets $< 25 \times 10^9$/L, respectively. Patients were retreated only if the WBC counts were $> 4 \times 10^9$/L and platelets $> 130 \times 10^9$/L. For severe gastrointestinal side-effects including nausea, vomiting, stomatitis and diarrhea, doses of Mitomycin-C and Adriamycin were held till recovery; cis-platinum doses were reduced by 50%. For renal toxicity, if serum creatinine values were between 1.6 and 2.0 mg/dl, doses of cis-platinum and CCNU were reduced by 33%; for values >2.0 mg/dl, cis-platinum doses were held and CCNU dose was reduced by 50%. For cardiac toxicity, Adriamycin doses were discontinued; for allergic reactions, cis-platinum and Bleomycin doses were discontinued; for auditory toxicity cis-platinum doses were discontinued and finally for pulmonary toxicity, Bleomycin doses were discontinued. Patients remained on treatment unless there was documented progression of disease or unmanageable toxicities. After progression through MAP therapy, patients were re-evaluated and if still eligible were registered to the second study step to receive sequential Bleomycin and CCNU treatment. Patients were then followed on treatment till documented disease progression, relapse or unmanageable side-effects. Anti-tumor response was evaluated before every treatment cycle and a complete response (CR) was defined as absence of any clinically detectable tumor in the body for at least four weeks. Partial response (PR) was defined according to the following criteria:

(1) A reduction in tumor mass by at least 50% of the product of the longest perpendicular diameters of the most clearly measurable mass lesion.
(2) If hepatomegaly was the primary indicator lesion, a reduction of the sum of the liver measurements below each costal margin at the mid-clavicular lines and xiphoid process by at least 30%.
(3) No increase in other lesions or development of new malignant lesions for at least four weeks.

Stable disease was defined as lesions that were not CR or PR and there was no greater than a 25% increase in any measurable lesion. Progressive disease was defined as any measurable lesion that increased in size to greater than 25% as compared with baseline measurements or the appearance of any new malignant lesions.

Toxicity assessments, efficacy evaluations and serum chemistry tests were performed prior to every cycle of therapy. The blood counts were obtained weekly.

Statistical analysis

The principal end-point of this study was tumor response. The original design was to enter at least 15 evaluable patients to receive the MAP treatment followed by 5 additional evaluable patients added for each response seen in the first 15 patients (up to a maximum of 15 additional patients). The study design was intended to enter fewer patients if the study regimen was inactive while allowing for added patient accession and a correspondingly more precise estimate of the response rate if the treatment was active. Accrual for this study was open from April 11, 1983 to October 31, 1990. Accrual was steady at a rate of 4 patients per year. The study was terminated in 1990 after accruing twenty-five patients, 5 patients short of its original accrual goal. Accrual slowed as the study aged and hence it was decided to terminate the study early rather than let it linger forever. As a result, the confidence intervals may be up to 4% points wider than what they would have been had we accrued 30 patients on this study. The Kaplan-Meier method [10] was used to obtain survival estimates and the Brookmeyer and Crowley method [11] was used to obtain confidence intervals for the medians of the survival times.

Results

Of the twenty-five patients entered from the 12 ECOG institutions, 20 patients were properly registered and of those, 19 were evaluable for toxicity and response assessments on MAP treatment. The five patients excluded from the primary analysis were either ineligible ($n = 3$) or did not receive their assigned treatment ($n = 2$). The three ineligible cases were due to the following: previous treatment with study drugs, history of a previous malignancy (lymphoma) and for the third there was no pretreatment data and furthermore this patient was lost to follow-up after registration. Of the two patients who did not receive assigned treatment: one patient had inadequate ejection fraction as measured by MUGA scan after study entry and for the other patient there was lack of data reporting from the registering site. Only 2 patients subsequently received Bleomycin and CCNU and both were eligible for toxicity and response assessment. The patient characteristics are shown in Table 1. 60% of the patients were <60 years of age and 55% had squamous histology. Given the unique referral patterns to each institution and the rarity

Table 1 Patient characteristics ($N = 20$ patients)

Characteristic	No. (%)
Enrolled	20
Race	
White	13 (65)
Other	7 (35)
Age, years	
<60	12 (60)
≥60	8 (49)
Sex	
Male	10 (50)
Female	10 (50)
Performance status (ECOG)	
0	6 (30)
1	8 (40)
2	5 (25)
3	1 (5)
Prior therapy	
Unknown	12 (60)
None	3 (15)
Surgical resection	1 (5)
Radiation/Chemotherapy	4 (20)
Cell type	
Basaloid squamous cell	7 (35)
Squamous cell	11 (55)
Basaloid small cell	2 (10)
Differentiation	
Good	2 (10)
Moderate	9 (45)
Poor	9 (45)

Table 2 Toxicities ($N = 20$)

Toxicity	Mild	Moderate	Severe	Life-threatening
Vomiting	3	11	2	–
Diarrhea	1	2	–	–
Infection	–	3	–	–
Skin/Mucositis	4	2	1	–
Neurologic	5	3	–	–
Respiratory	1	–	–	–
Genitourinary	5	–	–	–
Hematologic	2	5	7	2
Alopecia	–	4	–	–
Edema	1	–	–	–
Other*	3	4	2	–
Worst toxicity Experienced	1	8	8	2

*Other toxicities included: one case of grade 3 cardiac toxicity and grade 2 alopecia, one case of grade 2 alopecia and chills, one case of grade 2 alopecia, fatigue and malaise, one case of grade 2 alopecia and grade 1 edema and fever and grade 3 leg cramps, and one case of grade 1 cardiac toxicity and edema.

of these tumors, 60% patients had unknown prior treatments since they presented for the first time to the participating institutions. 95% of patients had ECOG PS ≤ 2. Eligible patients were treated with MAP until progression of disease or relapse. At this point, these patients were re-evaluated and if still eligible were treated with Bleomycin and CCNU until progression or relapse. Of the twenty properly registered patients, only 2 patients were eligible for registration to the second step (Bleomycin and CCNU).

The toxicities of the combination therapy are shown in Table 2. Ten patients experienced grade 3 or higher toxicity which were mostly hematologic. The next most prominent toxicity was grade 2 vomiting. Of the two patients treated with Bleomycin and CCNU, one patient experienced grade 3 vomiting and grade 2 alopecia and the other had mild fever. Both patients had grade 2 skin rash and mucositis and grade 1 myelosuppression. Two patients entered the study with elevated creatinine and BUN and both patients had worsening BUN and creatinine parameters while on study. One of these patients, experienced renal insufficiency 5 weeks after the completion of MAP therapy and it was felt likely due to new renal metastases. The other patient experienced progressive elevation in BUN while the dose of cis-platinum was reduced. Hematologic toxicity was dose-limiting in two patients. One patient had grade 4 leukopenia (WBC 600 /mm^3) on day 15 of cycle 1. Blood count recovery was noted 2 days later and the patient received appropriate dose reduction for the subsequent cycle of therapy. Another patient had grade 4 thrombocytopenia (platelets 15,000 mm^3) on day 14 of cycle 5. Platelet count recovery was noted on day 27. The toxicities in this study were graded based on the ECOG grading criteria. Table 3 depicts the comparison between ECOG (criteria used in this study) and Common Toxicity Criteria version 3 (currently used) [12] for some of the commonly seen adverse events in this study.

Twelve of the twenty eligible patients had a partial response (60%; 95% CI {36–81%}). There were no complete responses observed. Of the 12 responders, nine patients relapsed at the time of the study's final report (March 1992) and went off study at that time, hence they did not have an opportunity to move to the second study step. Two patients who had a response died without confirmation of progressive disease. And one patient who had a response showed evidence of continued response until February 1990, which was the last date of known remission for that patient. Of the remaining 8 patients, six patients progressed without ever responding to treatment, one patient, who was unevaluable for response, died and another patient who progressed on therapy died without confirmation of progressive disease. There were only 2 patients who were eligible to receive Bleomycin and CCNU, of these patients one died a year after registering in this step without confirmation of progression while the other progressed within one month of therapy. It is important to note that even amongst this small subset of patients, responses were seen in all histologic subtypes as well as in

all histologic grades. Seventeen of the 20 patients have died. The median survival time was 15 months (95% CI {6–20 months}). The median time to disease progression or death whichever came first was 8 months (95% CI {4–9 months}) in the 19 patients evaluable for analysis. The 6 and 12-month progression free rates were 58 and 26%, respectively. The median time to relapse of the 12 patients who initially had a partial response to MAP therapy was 6 months.

Discussion

Locally advanced, recurrent or metastatic anal carcinoma represents a clinically significant problem, the management of which remains the subject of some controversy. Although the current data suggests radical surgery to be the sole salvage treatment able to provide some chance of cure, some authors have reported disappointingly low success rates [13]. The purpose of this trial was to investigate the effectiveness and tolerability of the combination regimen of MAP chemotherapy in patients with metastatic or locally advanced anal canal cancer, and to determine the anti-tumor activity of the combination of Bleomycin and CCNU as second line treatment in patients with anal cancer who have failed primary MAP therapy.

MAP combination chemotherapy with or without Bleomycin has been widely tested in a variety of malig-

Table 3 Toxicity criteria—ECOG and Common Toxicity Criteria (CTC) version 3
3.1. Common hematologic toxicity

	Grade					
	Neutropenia (ANC/mm^3)		Thrombocytopenia (/mm^3)		Anemia (Hgbgm/dl)	
Toxicity grade	ECOG	CTC	ECOG	CTC	ECOG	CTC
0	1900	–	≥13,000	–	≥11	
1	<1900–1500	<LLN–1500	<130,000–90,000	<LLN–75,000	11–9.5	<LLN–10
2	<1500–1000	<1500–1000	<90,000–50,000	<75,000–50,000	<9.5 or symptomatic	10–8
3	<1000–500	<1000–500	<50,000–25,000	<50,000–25,000	Requires transfusion	8–6.5
4	<500	<500	<25,000	<25,000	–	<6.5
5	–	Death	–	Death	–	Death

3.2. Gastrointestinal toxicity

	Grade					
	Nausea		Vomitting		Diarrhea	
Toxicity grade	ECOG	CTC	ECOG	CTC	ECOG	CTC
1	Mild	Loss of appetite without alteration in eating habits	Mild	1 episode in 24 hr	No dehydration	Increase of <4 stools/day over baseline
2	Controllable or transient	Decreased oral intake, no significant wt loss, malnutrition, dehydration, IVF indicated <24 hr	Controllable or transient	2–5 episodes in 24 hr, IVF indicated <24 hr	Dehydration	Increase of 4–6 stools/day over baseline, IVF indicated <24 hr, not interfering with ADL
3	Intractable requiring parenteral fluids	Inadequate oral/fluid intake, tube feedings/TPN indicated ≥24 hr	Intractable requiring parenteral fluids	≥6 episodes in 24 hr, IVF or TPN indicated ≥24 hr	Grossly bloody diarrhea	Increase of ≥7 stools/day over baseline, IVF indicated ≥24 hr, hospitalization, interfering with ADL
4	–	Life threatening consequences	–	Life threatening consequences		Life threatening consequences Hemodynamic collapse
5	–	Death	–	Death	–	Death

3.3. Respiratory and renal Toxicity

	Grade					
	Respiratory		Renal (Serum creatinine mg/dl)		Renal (Proteinuria)	
Toxicity grade	ECOG	CTC	ECOG	CTC	ECOG	CTC
0	None	–	≤ 1.2	–	–	–
1	25–50% decrease in DLCO/VC, mild symptoms	DOE but can walk 1 flight of stairs without stopping, 10–25% decrease in VC	1.3–2	>ULN–1.5 × ULN	1 +	1 + .15-1 g/24 h
2	>50 %decrease in DLCO/VC, moderate symptoms	DOE, unable to walk 1 flight of stairs, 25–50% decrease in VC	2.1–4	>1.5–3 × ULN	2–3 +	2−3 + 1–3.5 g/24 hr
3	Requires intermittent oxygen	Dyspnea with ADL, 50–75% decrease in VC	>4	>3–6 × ULN	4 +	4 + >3.5 g/24 hr
4	Requires continuous oxygen or assisted ventilation	Dyspnea at rest, intubation or ventilator indicated, >75% decrease in VC	Clinical uremia	>6 × ULN	–	Nephrotic Syndrome
5	–	Death	–	–	–	Death

3.4. Skin/Mucous membrane and Infection

	Grade					
	Skin		Mucositis/stomatitis		Infection	
Toxicity grade	ECOG	CTC	ECOG	CTC	ECOG	CTC
1	Transient erythema, pigmentation, atrophy	Mild erythema, desquamation; atrophy, pigmentation	Pain, erythema	Erythema	No active treatment required	–
2	Vesiculation, subepidermal fibrosis	Moderate erythema or eruption, intervention indicated, interfering with function	Ulcers, can eat	Patchy ulceration or pseudomembranes	Requires active treatment	Localized, local intervention indicated
3	Ulceration, necrosis	Ulcerative changes interfering with function	Ulcers, cannot eat	Confluent ulceration, bleeding with minor trauma	Debilitating	IV medications or IR/ operative intervention indicated,
4	–	Generalized exfoliative, ulcerative or bullous dermatitis, spontaneous bleeding or disabling, life threatening		Tissue necrosis, spontaneous bleeding, life threatening	Life threatening	Life threatening (hypotension,septic shock, acidosis)
5	–	Death	–	Death	–	Death

3.5. Neurotoxicity

	Grade			
	Neurotoxicity Peripheral neuropathy		Neurotoxicity Central Nervous System	
Toxicity grade	ECOG	CTC	ECOG	CTC
0	–		–	
1	Decreased DTR, mild parasthesia	Asymptomatic, detected on exam/tests only	Mild anxiety, lethargy, depression, headache	Transient confusion
2	Loss of DTR, severe parasthesia, mild motor loss	Symptomatic (sensory/motor) not interfering with ADL	Severe anxiety, moderate depression, headache, somnolence, tremor, hyperactivity	Confusion, extrapyramidal, involuntary movements, somnolence, tremors not interfering with ADL
3	Severe weakness, disabling sensory loss, severe nerve pain, bowel, bladder dysfunction	Symptomatic (sensory/motor) interfering with ADL	Confusion, severe depression, intractable headaches, spinal cord dysfunction, bed bound	Confusion/delirium, Extrapyramidal, involuntary movements, somnolence, tremors interfering with ADL
4	Respiratory dysfunction, paralysis, bed bound	Life threatening, disabling	Seizures, suicidal, coma	Disabling or Harmful to self/others, hospitalization indicated
5	–	Death	–	Death

nancies and the toxicities of this combination therapy have been well established [18–20]. The combination therapy has been effective for a variety of malignancies including non-small cell lung cancer, esophageal and gastric cancer as well as soft tissue sarcomas [14–24]. The toxicities of MAP chemotherapy include moderate to severe myelosuppression (<35%) although severe myelosuppression is seen in less than 10% of patients. The length of neutropenia is typically less than 10–14 days and usually there is recovery without the need for growth factor support. Nonhematologic toxicity is usually mild and includes nausea/vomiting which can be controlled with standard anti-emetics, mucositis/skin rash typically attributed to Mitomycin-C and Bleomycin and moderate alopecia. In this study, the incidence of moderate-severe hematologic toxicity was around 35%, which is in agreement with studies published with this regimen for other solid tumors [18–20, 23]. Of note, in our population, four of the 20 patients had prior pelvic irradiation, this may have also compromised marrow function or response to chemotherapy. Direct toxicity or tolerance comparison between this regimen and other currently used regimens is difficult due to the different toxicity grading system used in this study. Remarkably, the response rate in this study of 60% is consistent with other combination chemotherapy regimens for metastatic anal cancer; however, it was disappointing to see that there were no complete responses. The combination of MAP is active for squamous cell carcinomas of the anus; however, its tolerability may be most applicable for patients who have had minimal prior therapy. The response to Bleomycin and CCNU is difficult to assess in this study, as there were only two patients who crossed over to get this treatment. One patient died a year after registration but without confirmation of disease progression and the other progressed within one month on treatment. Hence, this study confirms the moderate activity of MAP regimen for anal carcinoma.

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