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Phase II study of combination bleomycin, vincristine and high-dose methotrexate (BOM) with leucovorin rescue in advanced squamous cell carcinoma of the anal canal

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Summary. Fifteen patients with advanced squamous cell carcinoma of the anal canal were treated with a combination of bleomycin, vincristine, and high-dose methotrexate (BOM) with leucovorin rescue. Three out of twelve patients with measurable disease had objective responses of 1, 2, and 5 months. Five of the fifteen patients had severe or life-threatening complications as a result of this treatment regimen. The narrow therapeutic index of the BOM therapy makes it a less than ideal drug combination for the treatment of advanced squamous cell carcinoma of the anal canal.

Introduction

Squamous cell carcinoma of the anal canal accounts for 1%–2% of all colorectal malignancies [13]. Primary treatment of this malignancy has so far consisted of surgery requiring an abdominoperineal resection, but recently treatment with radiation with or without chemotherapy has been advocated [2, 4, 7, 8, 11, 13]. The treatment for advanced nonresectable or metastatic disease includes chemotherapy and/or radiotherapy [2, 6, 8, 10]. The most widely used chemotherapeutic agents for squamous cell carcinoma have been methotrexate and bleomycin [1, 5, 9, 14]. Vincristine has also proven to be of value in these tumors [1, 5, 14].

Few reports concerning the results of chemotherapy in advanced squamous cell carcinoma of the anal canal have been published [2, 6, 8, 10], and therefore we find it of interest to report our experience at Roswell Park Memorial Institute. A protocol of combination bleomycin, vincristine, and high-dose methotrexate (BOM) with leucovorin rescue was implemented in August 1977 and discontinued in August 1982.

Materials and methods

Patient Characteristics. Fifteen patients with biopsy-proven locally advanced or metastatic squamous cell carcinoma of the anal canal were eligible for this protocol. Table 1 gives information concerning each patient's sex, age, performance status, disease-free interval, treatment prior to BOM chemotherapy, and the monitoring lesions. Of the 15 patients, 3 had nonmeasurable but biopsy-proven lesions (2 had pelvic disease and 1 pulmonary metastases). For entrance onto the BOM trial patients were required to have WBC $>5000/mm^3$, platelets $>100\,000/mm^3$, creatinine clearance >60 cc/min, life expectancy >90 days, and performance status 0–3 according to the Eastern Cooperative Oncology Group classification (Table 1).

Treatment schedule. A course of chemotherapy was defined as a continuous infusion of bleomycin 10 mg/m^2 in 1000 cc D5W over 24 h for 5 days. This was followed by vincristine 1.2 mg/m^2 by IV push (maximum dose 2.0 mg). Following a rest period of 22 h, methotrexate 75 mg/m^2 was administered as an IV push and then 175 mg/m^2 IV in 1000 cc D5W over 12 h. Leucovorin 15 mg was given by IV push every 6 h for six doses after completion of the methotrexate infusion. This regimen was repeated every 4 weeks. The above regimen was based on data that revealed a superior response in testicular carcinoma to continuous-infusion bleomycin versus IV push (61% complete response vs 26%) [12]. The combination of continuous-infusion bleomycin over 96 h followed by a 48-h rest and a 24-h infusion of methotrexate 250 mg/m^2 revealed a 60% response rate in patients with advanced head and neck tumors [3]. Therefore, the use of bleomycin as a cell-synchronizing agent with reversible block at the 5-G_2 boundary followed by a cell-cycle-specific agent appeared to be reasonable.

Dose reduction. All patients who had received prior radiotherapy of more than 40 Gy had the first dose of all chemotherapy reduced by one third. Subsequent courses were given at the full dose if there was no myelosuppression. For myelosuppression the dose of methotrexate was reduced as follows: mild toxicity (WBC 2500–4000/mm^3 and/or platelets 75 000–150 000/mm^3), 40% reduction, moderate toxicity (WBC 1500–2499/mm^3 and/or platelets 40 000–75 000/mm^3), 60% reduction. No treatment was given in the presence of severe myelosuppression (WBC $<1500/mm^3$ and/or platelets $<40\,000/mm^3$). If moderate to severe gastrointestinal toxicity as defined by the Eastern Cooperative Oncology Group (ECOG) occurred the dose of methotrexate was reduced by 20%. If patients had a creatinine clearance <50 cc/min or a serum bilirubin >3.0 mg% no methotrexate was given.

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Table 1. Patient characteristics

Patient	AGE (years)	Prior treatments	Recurrence-free interval (months)[c]	Performance status[d]	Monitoring lesion
1. Female	59		21	0	Inguinal node
2. Female	62		5	0	Inguinal node
3. Female	66	RT[b]	1	2	Inguinal node
4. Female	56		12	0	Inguinal node
5. Female	54	RT	3	1	Inguinal node
6. Female	71	RT	17	0	Inguinal node
7. Female	60	HAI[a]	7	0	Liver
8. Female	47		0	0	Liver
9. Male	62	RT	5	2	Lung
10. Female	48	RT	0	1	Pelvis
11. Female	58	RT	8	1	Supraclavicular node
12. Female	51		33	1	Supraclavicular node
13. Female	72		0	1	Nonmeasurable disease
14. Female	62		0	2	Nonmeasurable disease
15. Female	46	RT + chemotherapy	60	1	Nonmeasurable disease

[a] Hepatic artery ligation
[b] External radiation therapy
[c] From time of primary tumor diagnosis to metastasis
[d] 0 = normal and active; 1 = symptoms but ambulatory; 2 = in bed < 50% of time; 3 = in bed > *50% of time; 4 = bedridden*

No patients were given a total dose of more than 150 mg/m^2 of bleomycin. The vincristine dose was reduced by 50% if mild neurologic toxicity with numbness or paresthesias occurred, but if paresis or muscle weakness occurred no vincristine was given. The vincristine was reduced by 50% if the serum bilirubin was 1.5–3.0 mg%, and by 75% if the bilirubin was >3.0 mg%.

Response definitions included: *Complete response*, disappearance of all evidence of tumor; *partial response*, >50% decrease in the summed products of the perpendicular diameters of bidimensionally measurable lesions; *stable disease*, decrease in tumor size but by less than a partial response, with no appearance of new lesions; and *progression*, an increase in size of recognizable tumor by 25% and/or the appearance of new lesions. The patients with nonmeasurable disease were evaluated for toxicity only.

Results

The results concerning the number of treatments, responses, toxicity, and survival are given in Table 2.

Among the 12 patients who had measurable disease, 3 had partial responses lasting 1, 2 and 5 months. One of these patients had mild hematologic toxicity, while the other two patients had mild nausea as their only side effect.

Table 2. Results of BOM treatment in advanced squamous cell carcinoma of the anal canal

Patient	AGE (years)	Before BOM treatment	Number of BOM courses	Result	Survival after BOM treatment (months)
4. Female	56		3	Partial response (2 months)	32
2. Female	62		9	Partial response (5 months)	19
1. Female	59		1	Partial response (1 months)	5
7. Female	60	HAL[a]	11	Progression	24
13. Female	72		8	Progression	7
6. Female	71	RT[b]	2	Progression	9
8. Female	47		2	Progression	9
10. Female	48	RT	2	Progression	8
11. Female	58	RT	2	Progression	6
14. Female	62		3	Progression	12
15. Female	46	RT + chemotherapy	2	Progression	10
12. Female	51		1	Death before evaluation	1
3. Female	66	RT	1	Death before evaluation	1
9. Male	62	RT	1	Death before evaluation	1
5. Female	54	RT	1	Death before evaluation	1

[a] Hepatic artery ligation
[b] Radiation therapy

Five patients had disease progression. This occurred in four of these patients after 2 courses and in one patient after 11 courses. One of these five patients had no toxic symptoms except nausea; two patients had mild hematologic toxicity, one had mild gastrointestinal and hematologic toxicity, and one patient had mild renal impairment (serum creatinine 1.3–2.0 mg%).

Four other patients had severe complications connected with their first course of chemotherapy. One patient developed a monilia sepsis in relation to severe myelosuppression. The hematologic toxicity was reversible, but the patient died of a massive upper gastrointestinal hemorrhage 6 weeks after initiation of the BOM treatment. A second patient, without any signs of myelosuppression, died in septic shock 5 weeks after initiation of the BOM therapy. Two other patients experienced severe, nonreversible myelosuppression connected with their first course of BOM treatment. Both patients died of sepsis; in one of them this was combined with epidermolysis. All these patients with complications died within 2 months after beginning the BOM chemotherapy program.

Two of the three patients with nonmeasurable disease showed signs of progressive disease after three and eight courses of BOM chemotherapy. One patient had mild hematologic toxicity and one had mild neurologic toxicity. The third patient had severe gastrointestinal toxicity during the second course of chemotherapy with severe diarrhea and vomiting, whereupon the treatment was discontinued.

The median survival of the 15 patients was 8 months from the start of the BOM chemotherapy regimen with a range of 1–32 months.

Discussion

Chemotherapy in combination with radiotherapy appears to be a possible alternative to surgery for the treatment of primary squamous cell carcinoma of the anal canal [4, 11]. In small series of patients with advanced squamous cell carcinoma of the anal canal, chemotherapy with radiotherapy has been shown to produce responses [6, 7, 10].

In the present series of 15 patients with advanced squamous cell carcinoma, 3 of 12 patients with measurable lesions responded to therapy. However, the responses were of relatively short duration. All three patients who responded to the BOM chemotherapeutic regimen had had no prior treatment apart from their primary surgery. They all had a zero performance status, and none of these patients had any severe side effects of the treatment.

In contrast, five of six patients who had received prior radiotherapy and/or chemotherapy, either as part of their primary treatment or for advanced disease, and who had a performance status of 1 or more had severe side effects of the BOM regimen. Ultimately, four patients died of causes related to their first treatment course. Death was due to severe hematologic toxicity and sepsis in three of the four patients.

All 15 patients in this study showed progression or severe to lethal toxicity within 1 year after the BOM treatment was started. This confirms the poor prognosis observed by other authors [6] for patients with advanced squamous cell carcinoma of the anal canal.

The BOM treatment induced an objective response in 25% of the patients with advanced squamous cell carcinoma of the anal canal in the present study. However, the responses were of short duration and there was a high incidence of severe drug-related toxicity. We feel that the narrow therapeutic index of the BOM regimen described limits its use in patients with advanced squamous cell carcinoma of the anal canal.

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