Eur J Cancer, Vol. 26, No. 6, pp. 748–749, 1990.
Printed in Great Britain

0277–5379/90$3.00 + 0.00
Pergamon Press plc

Treatment of Small-cell Carcinoma of the Cervix with Weekly Combination Chemotherapy

Imad A. Tabbara, William A. Grosh, Willie A. Andersen, Peyton T. Taylor, Seung S. Hahn and F. Marc Stewart

Three patients with small-cell carcinoma of the cervix entered a pilot study of combination chemotherapy with agents that are not cross-resistant. Two patients had local disease and the third had extensive metastatic disease of the liver. The regimen consisted of weekly chemotherapy for 16 weeks with cisplatin, vincristine, methotrexate, doxorubicin, cyclophosphamide and etoposide followed by radiotherapy and/or surgery. The two patients with local disease achieved a pathological complete response, with no evidence of disease at 24 months and 15 months from diagnosis. The third patient achieved a partial response and is alive at 13 months with progressive disease. Side-effects were tolerable.
Eur J Cancer, Vol. 26, No. 6, pp. 748—749, 1990.

INTRODUCTION

SMALL-CELL carcinoma (SCC) has been reported to involve extrapulmonary organs including larynx, esophagus, pancreas, breast and cervix [1]. SCC of the cervix, which accounts for a small proportion of cervical cancer, has a variable frequency: 14% [2], 4% [3], 0.2% [4] and 2.7% [5]. SCC of the cervix can also complicate pregnancy [6–8]. Several investigators [1–3, 5, 9] have concluded that SCC of the cervix is associated with a high frequency of recurrence and limited survival. Therapy for SCC of the cervix is primarily surgical or radiological or a combination. Experience with systemic chemotherapy is limited because of the assumption that this disease may not be as chemosensitive as the pulmonary neoplasm.

Based on the MACOP-B regimen in aggressive large cell lymphoma [10], this pilot study of previously untreated patients with SCC of the cervix aimed to establish whether initial aggressive treatment with alternating agents, which were not cross resistant, in a weekly schedule followed by radiotherapy and/or surgery would result in a high response rate with acceptable toxicity.

PATIENTS AND METHODS

Patients

The trial started in October 1986, as a prospective non-randomized study and was approved by the university's Human Investigation Committee. Written informed consent was obtained from the patients before starting chemotherapy and only patients aged 18 years or older were considered. Eligibility criteria included histological or cytological proof of SCC, no previous chemotherapy or radiotherapy. Karnofsky performance status of 30% or more, measurable or evaluable evidence of disease (physical and/or radiological), and adequate renal function (serum creatinine below 1.5 mg/dl).

Histological and/or cytological specimens were reviewed in our pathology department and were diagnostic of SCC. Patients with brain metastasis at presentation were eligible and could receive radiotherapy to the brain (3000 cGy in ten fractions) starting during week 1 with chemotherapy. Patients with severe congestive heart failure, cardiac arrhythmias requiring medical treatment or recent myocardial infarction (within the last 3 months) were excluded.

Pretreatment evaluation included history and physical examination, hemogram, metabolic profile, liver function tests, bone marrow biopsies and aspirates, bilateral, posterior iliac crest, chest X-ray, bone scan and computerized tomography (CT) of the head, chest, abdomen and pelvis.

Treatment

The chemotherapy protocol (POMACE) is summarized in Table 1. All chemotherapy was given in an outpatient setting except for cisplatin, which required overnight stay for hydration and mannitol diuresis. The doses and schedule of each agent were selected to prevent severe myelosuppression, renal toxicity and delay in administering chemotherapy.

The dose of cyclophosphamide, doxorubicin and etoposide was reduced by half if the absolute neutrophil count was between 500 and 1000/μl, and treatment with these agents was delayed a week if the count was less than 500. There was no dose reduction for low platelet count. The methotrexate dose was reduced by half if grade 2 (WHO) mucositis (ulcers) developed.

Correspondence to: I.A. Tabbara, M.D., University of Virginia School of Medicine, Box 502, Charlottesville, VA 22908, U.S.A.
I.A. Tabbara, W.A. Grosh, F.M. Stewart are at the Department of Internal Medicine, W.A. Andersen, P.T. Taylor are at the Department of Obstetrics and Gynecology and S.S. Hahn is at the Department of Radiotherapy, University of Virginia School of Medicine, Charlottesville, Virginia, U.S.A.

Table 1. POMACE regimen

Drug	Intravenous dose (mg/m²)	Weeks
Cyclophosphamide	350	1, 3, 9, 11
Doxorubicin	50	1, 3, 5, 7, 9, 11
Methotrexate	400*	2, 6, 10, 14
Vincristine	2 mg (total dose)	2, 4, 6, 8, 10, 12, 14, 16
Cisplatin	40†	5, 13, 15
Etoposide	80	7, 13, 15

*100 mg/m² intravenously followed by 300 mg/m² over 4 h. Folinic acid 15 mg orally every 6 h for six doses starting 24 h after methotrexate. Hydration with methotrexate consisted of 1 l dextrose/water and three ampoules $NaHCO_3$.

†Mannitol 12.5 g intravenously over 30 min before and after cisplatin. Hydration given as dextrose/half normal saline at 150 ml/h for 24 h. 2 h before and after cisplatin, infusion rate was increased to 300 ml/h.

Assessment

A hemogram was obtained and toxicity was recorded every week. Other laboratory evaluation was done as clinically indicated. Complete response (CR) was defined as the disappearance of all disease for at least 4 weeks. Partial response (PR) was greater than or equal to a 50% reduction of all measurable lesions with no newly identified lesions for 4 weeks. Stable disease implied a less than 50% reduction and less than 25% increase in all measurable disease with no appearance of new lesions for 4 weeks after completion of treatment. Patients were evaluated for response on the eighth week of chemotherapy. Those with CR, PR, or stable disease were continued on treatment. After completing the 16 weeks of chemotherapy, patients were restaged. Those with CR or PR with local disease received radiotherapy or radical surgery as required.

Patient 1 (*age 29/stage IIB at presentation*). CR (by cervical biopsy) and with no evidence of disease 24 months after diagnosis. Radiotherapy: first radium insertion 2750 cGy, to point A, pelvis w/midline shielding (4000 cGy in twenty fractions); second radium insertion, 3250 cGy to point A.

Patient 2 (*54/IB*). CR and with no evidence of disease at 15 months post diagnosis. CR was documented pathologically after total abdominal hysterectomy and bilateral salpingooophorectomy. This patient had marrow suppression that required a 25% dose reduction of myelosuppressive agents starting on week 7. She also had two episodes of fever (cause unknown) and neutropenia after the second and sixth week of treatment, which led to a 3 week delay in further chemotherapy.

Patient 3 (*40/IVB*). Extensive metastatic disease of liver at presentation. PR after 8 weeks of treatment. At end of chemotherapy, metastatic liver disease improved further (CT). This patient was then without disease progression for 9 weeks. She is alive with disease, despite the use of two salvage chemotherapies. This patient required a week's delay after the second week because of myelosuppression (WHO grade 4) and fever of unknown cause. Numbness and weakness in hands and feet led to the deletion of vincristine at weeks 14 and 16 in this case.

Side-effects

Mild to moderate stomatitis was seen in all three patients as well as controllable nausea and vomiting. There was no cardiotoxicity, nephrotoxicity or treatment-related death.

DISCUSSION

Surgical resection and/or radiotherapy have been the most common therapeutic approaches used in SCC of the cervix. Yamasaki *et al.* [9] reported ten patients with SCC of the cervix. Two of nine patients who had radical hysterectomy survived 5 years and both of them had stage I disease. Van Nagell *et al.* [3] reported a 5 year survival of 46% in forty-one patients treated with radiotherapy. Fifteen of their patients (37%) died within a year of diagnosis. Twenty-nine patients had stage I or II disease. Of the ten patients reported by Randall *et al.* [5], one with stage I disease was the only survivor at 5 years after receiving radiotherapy. The remaining nine included four with stage II, two with stage III and three with stage IV disease.

The design of our chemotherapy protocol was based on the proposal [11] that in malignant human cancer somatic cell mutation leads to the development of tumor cells resistant to chemotherapy and that the early use of effective cytotoxic agents which are not cross-resistant should produce the best results. In addition, we believe that the use of a lower dose of an individual cytotoxic agent in a more frequent (weekly) schedule and alternating myelosuppressive and non-myelosuppressive agents can lead to increased efficacy without severe hematological toxicity.

In our study, two out of three patients achieved CR and the overall objective response rate was 100%. All three patients are alive at 24, 15 and 13 months post diagnosis, with the first two patients being disease-free. These initial results are comparable to those reported by others [2, 3, 6, 8] and show that SCC of the cervix is chemosensitive. Our regimen was well tolerated and effective in this malignant neoplasm.

1. Remick SC, Hafez GR, Carbone PP. Extrapulmonary small cell carcinoma. A review of the literature with emphasis on therapy and outcome. *Medicine* 1987, **66**, 457–471.
2. Field CA, Dockerty M, Symmonds RE. Small cell cancer of the cervix. *Am J Obstet Gynecol* 1964, **88**, 447–451.
3. Van Nagell JR Jr, Donaldson ES, Wood EG, Maruyama Y and Utley J. Small cell cancer of the uterine cervix. *Cancer* 1977, **40**, 2243–2249.
4. Albores-Saavedra J, Larraza O, Pucell S, Martinez HAR. Carcinoid of the uterine cervix. Additional observations of a new tumor entity. *Cancer* 1976, **38**, 2328–2342.
5. Randall ME, Kim JA, Mills SE, Hahn SS, Constable WC. Uncommon variants of cervical carcinoma treated with radical irradiation. A clinicopathologic study of 66 cases. *Cancer* 1986, **57**, 816–822.
6. Jacobs AJ, Marchevsky A, Gordon RE, Deppe G, Cohen CJ. Oat cell carcinoma of the uterine cervix in a pregnant woman treated with *cis*-diamminedichloroplatinum. *Gynecol Oncol* 1980, **9**, 405–410.
7. Kodousek R, Guzarek F, Dusek J. Malignant 'apudoma' (argyrophil cell cancer) of the uterine cervix in a 24-year-old woman in pregnancy. *Cesk Pathol* 1976, **12**, 37.
8. Turner WA, Gallup DG, Talledo DE, Otken LB, Guthrie TH. Neuroendocrine carcinoma of the uterine cervix complicated by pregnancy: case report and review of the literature. *Obstet Gynecol* (Suppl) 1986, **67**, 80s–83s.
9. Yamasaki M, Tateishi R, Hongo J, Ozaki Y, Inoue M, Ueda G. Argyrophil small cell carcinomas of the uterine cervix. *Int J Gynecol Pathol* 1984, **3**, 146–152.
10. Klimo P, Connors JM. MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. *Ann Intern Med* 1985, **102**, 596–601.
11. Goldie JH, Coldman AJ, Gudanskas GA. Rationale for the use of alternating non-cross-resistant chemotherapy. *Cancer Treat Rep* 1983, **205**, 15–23.

Acknowledgement—We thank Connie D. Small for typing the manuscript.