Eur J Cancer Clin Oncol, Vol. 23, No. 9, pp. 1343–1347, 1987.
Printed in Great Britain

0277-5379/87$3.00+0.00

Mitomycin C is an Inactive Drug in the Third-Line Treatment of Hormone and Chemotherapy Refractory Breast Cancer

AD DEES,* JAAP VERWEIJ,* WIM L.J. VAN PUTTEN† and GERRIT STOTER*

*Department of Medical Oncology and †Department of Statistics, Rotterdam Cancer Institute, Rotterdam, The Netherlands

Abstract—*Mitomycin C (MMC) is rarely used in first-line chemotherapy for advanced breast cancer, although the drug is reported to be active. Treatment with MMC is usually reserved for second- or third-line treatment. We have given MMC as second- or third-line treatment to 59 patients. Fifty-six patients were evaluable for response. No complete and only 3 partial responses were observed for an overall response rate of 5%. The median time to progression was 2 months and median survival time was 6 months. In this retrospective study MMC is demonstrated to be inactive in third-line chemotherapy.*

INTRODUCTION

ADVANCED breast cancer is one of the malignancies where fairly high response rates can be achieved but no cure. In patients refractory to hormonal treatment or receiving chemotherapy up front, the chemotherapy of first choice mostly consists of a combination derived from the original Cooper regimen [1], such as the combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF). According to the literature the overall response rate of this combination is 50–60%, with 10–20% complete responses [2, 3]. All patients will show progression of disease afer a median time of 8–18 months [4, 5]. Therefore much attention has been given to second- and third-line chemotherapy.

Second-line chemotherapy usually consists of doxorubicin used as single agent or in combination with other drugs, yielding 20–40% responses with a median time to progression of 3–8 months [6–7]. The overall results of third-line chemotherapy are disappointing.

The cytotoxic alkylating antibiotic mitomycin C (MMC) has been extensively evaluated for its efficacy in metastatic breast cancer with controversial results [8–15]. In this paper we present the results of a retrospective analysis of the antitumor activity of MMC in patients treated in our institute.

Accepted 10 April 1987.
Address for correspondence: J. Verweij, Department of Medical Oncology, Rotterdam Cancer Institute, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands.

MATERIALS AND METHODS

Between 1980 and 1985, 343 patients with metastatic breast cancer were treated with chemotherapy.

Sixty-one of them were treated with MMC during the course of their disease. Five patients were rejected from this analysis, 2 because they had received MMC as first-line therapy, 3 because they died within 4 weeks afer the start of MMC. The remaining 56 patients were evaluable for response and toxicity. Patient characteristics are shown in Table 1. It can be seen that all patients had been extensively pretreated.

Forty-six patients received MMC i.v. at a dose of 5–10 mg/m^2 every 3–6 weeks, 30 of them at a dose of 10 mg/m^2 q 6 weeks. The remaining 10 were treated intra-arterially because of liver metastases (Table 2). Treatment with MMC was continued until proven progression of disease.

Indicator lesions were assessed by means of physical examination, X-rays and CT-scans. All patients had lesions which could be measured in two dimensions. Bone metastases were not considered measurable. The dominant sites of metastases and numbers of organs involved are summarized in Table 3.

The response to treatment was evaluated after 2 courses of MMC. Patients with rapidly progressive disease after only 1 course were considered evaluable and classified as progression. The response evaluation was performed according to the outlines published by the WHO [16]. CR denotes for complete response, PR partial response, SD stable disease and PD progressive disease.

Table 1. Patient characteristics (n = 56)

Menopausal status	
pre	26 (46%)
post	30 (54%)
Age (years)	
median	52.5
range	33–80
Performance status (Karnofsky index)	
median	80%
range	60–100%
Previous chemotherapy	
No. of different drugs	
3	13 (23%)
4	30 (54%)
5	12 (21%)
> 5*	1 (2%)
cyclophosphamide	56 (100%)
methotrexate	54 (96%)
5-FU	56 (100%)
doxorubicin	45 (80%)
vinca alkaloids	12 (21%)

*One patient was treated with 7 cytostatic drugs.

Table 2. Administration of MMC

Second-line	13 (23%)
Third-line	43 (77%)
Intravenously	46 (82%)
Intra-arterially	10 (18%)
Dosage in mg/m^2	
5	8
6	1
8	1
10	46 (82%)
Interval	
3 week	23 (41%)
6 week	33 (59%)
Other cytostatic drugs combined with MMC	
vinca alkaloids	9 (16%)
doxorubicin	6 (11%)
none	41 (73%)
Number of courses MMC	
1	14 (25%)
2	23 (41%)
3	8 (14%)
≥4	11 (20%)

RESULTS

Sixty-six per cent of the patients treated with MMC received 1 or 2 courses. Twenty per cent were treated with 4 courses or more (Table 2). The median number of courses was 2. Treatment with MMC was well tolerated. Toxicity consisted of nausea, vomiting and myelosuppression, especially thrombocytopenia. Severe cardiopulmonary or renal side effects were not observed.

Table 3. Metastases

Number of organs involved	
1	15 (27%)
2	20 (36%)
≥ 3	21 (37%)
Sites of metastases	
liver	26 (46%)
skin	26 (46%)
bone	22 (39%)
lung	17 (30%)
pleura	13 (23%)
other sites	23 (41%)

Table 4. Results

Response	Number of patients	Percentage of patients
CR	0	
PR	3	(5)
SD	13	(23)
PD	40	(72)

Among the 56 treated patients no CR and only 3 PR (5%) were observed. Thirteen patients had SD, and 40 showed PD (Table 4). The time to progression and survival time are shown in Fig. 1. The median time to progression was 2 months and the median survival 6 months.

Six patients were treated in second-line combination therapy with MMC and doxorubicin. Median time to progression in this small group was 7 months, median survival was 11 months. One of them achieved PR. She was 44 years old with extensive metastases in skin, pleura and pericardium, refractory to hormone and CMF therapy. Oestrogen and progesterone receptors were unknown. Time to progression was 9 months and survival time 13 months.

The 2 other women achieving PR were treated with single agent MMC as third-line therapy. The first patient achieving a PR was 54 years old. Her metastases were located in lung and skin. She failed on hormone therapy, but had SD on CMF followed by doxorubicin. The PR on MMC 10 mg/m^2 q 6 weeks lasted for 5 months and survival time was 7 months. The second patient was 57 years old and was treated with MMC intra-arterially and intravenously because of metastases in liver, bone and pleura.

Previous treatment consisted of hormone therapy for 2 years followed by CMF and doxorubicin. Time to progression was 8 months and survival 14 months.

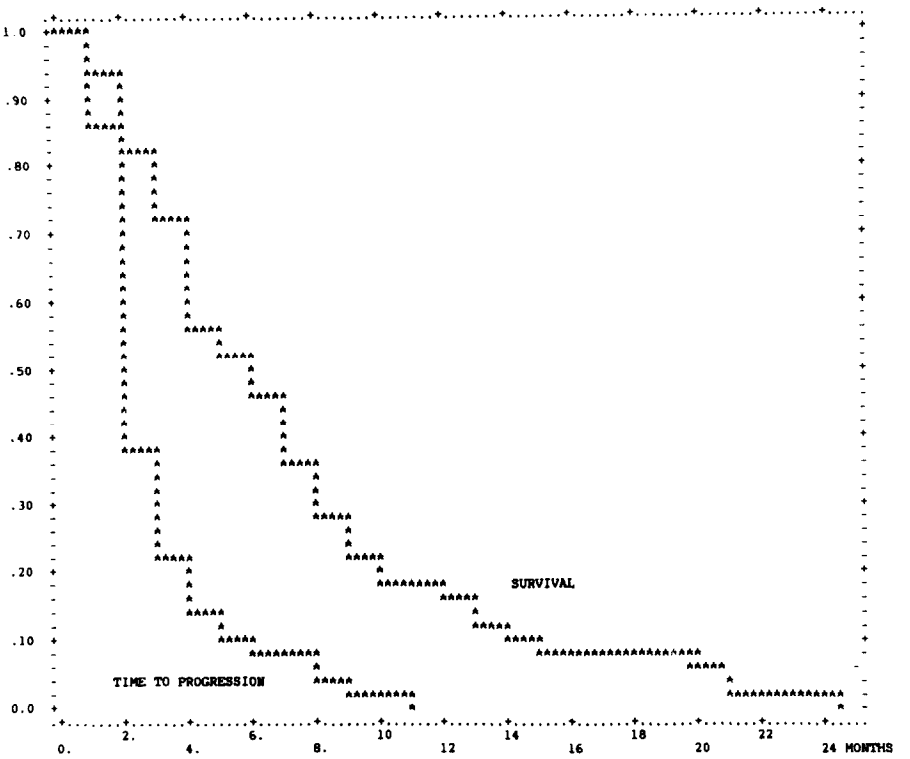

Fig. 1. Survival time and time to progression

DISCUSSION

In this study MMC was found to be inactive as third-line chemotherapy with only 2 PR of short duration. The available literature indicates that MMC is effective in first-line chemotherapy for advanced breast cancer. The cumulative data of 15 studies on single agent MMC in first- and second-line treatment, including a total of 541 patients, gave a mean response rate of 24%, duration of response was brief (3–4 months) and CR was rarely observed [3, 8, 17]. Most combination chemotherapy regimens in first-line treatment with MMC included doxorubicin. Response rates of 40–60% were reported with a median duration of 8–15 months [7, 18, 19]. A few studies including other drugs but without doxorubicin yielded the same percentage of response, but of only 5–7 months duration [20, 21], while no benefit was observed when compared to the CAF and CMF regimens or to single agent doxorubicin [7, 22, 23].

The role of MMC in second-line chemotherapy is difficult to assess because of the combination with other drugs, such as doxorubicin. Response rates of 23–34%, with a median duration of 4–9 months were reported [24–26]. But MMC does not seem to contribute to the effect of other agents. In a randomized study Anderson *et al.* [27] did not find any advantage of the addition of MMC to doxorubicin. Interesting was the fact that they discontinued entrance to a single agent MMC study arm after 12 patients because of unacceptable toxicity, which is in complete contrast to our data and probably due to the dose of 20 mg/m^2 that they used. Another reason for this discontinuation was the suggestion of minor efficacy, which is confirmed by our data. Results of second-line combination therapy without doxorubicin were slightly less, with a 18–31% response rate an 3–6 months response duration [28–30]. Other second-line studies are difficult to evaluate because of the small number of patients [31, 32] or the inclusion of patients without prior chemotherapy [33–35].

Studies on third-line MMC treatment are rarely performed. Creech reported a single agent study with MMC in 90 patients. Response rate was 16% and time to progression 4 months. Overall survival time was 6 months. All responses concerned patients with soft tissue and lung metastases [36]. Two other studies observed marginally efficacy for MMC with 5 and 9% responses [37, 38].

Our retrospective analysis shows that MMC is of no value in third-line treatment of metastatic breast cancer. Responses were of short duration and survival of all patients was only 6 months.

Furthermore, the risks of MMC, especially its cardiotoxicity after the use of doxorubicin, are considerable [15, 36, 39]. Treatment in this phase of disease should be limited to supportive measures.

REFERENCES

1. Cooper R. Combination chemotherapy of hormone-resistant breast cancer. *Proc Am Assoc Cancer Res* 1979, **10**, 15.
2. Henderson C, Canellos GP. Cancer of the breast: the past decade. *N Engl J Med* 1980, **302**, 78–90.
3. Lenaz L. Mitomycin C in advanced breast cancer. *Cancer Treat Rev* 1985, **12**, 235–249.
4. Canellos GP, de Vita VT, Gold GL *et al.* Combination chemotherapy for advanced breast cancer. Response and effect on survival. *Ann Intern Med* 1976, **84**, 389–392.
5. Carbone PP, Bauer M, Band P, Tormey D. Chemotherapy of disseminated breast cancer. *Cancer* 1977, **39**, 2916–2922.
6. Brambilla C, De Lena M, Rossi A, Valagussa P, Bonadonna G. Response and survival in advanced breast cancer after two non-cross-resistant combinations. *Br Med J* 1976, **1**, 801–804.
7. Amiel SA, Stewart JF, Earl HM, Knight RK, Rubens RD. Adriamycin and mitomycin C as initial chemotherapy for advanced breast cancer. *Eur J Cancer Clin Oncol* 1984, **20**, 631–634.
8. Crooke ST, Bradner VT. Mitomycin C: a review. *Cancer Treat Rev* 1976, **3**, 121–139.
9. Doll CD, Weiss RB, Issell BF. Mitomycin: ten years after approval for marketing. *J Clin Oncol* 1985, **3**, 276–286.
10. Hortobagyi GN. Mitomycin C in breast cancer. *Semin Oncol* 1985, **12** (Suppl 6), 65–70.
11. Di Constanzo F, Gori S, Tonato M *et al.* Vindesine and mitomycin C in chemotherapy refractory advanced breast cancer. *Cancer* 1986, **57**, 904–907.
12. Creech RH, Catalino RB, Shah MK *et al.* An effective low dose mitomycin rgimen for hormonal and chemotherapeutic refractory patients with metastatic breast cancer. *Cancer* 1983, **51**, 1034–1040.
13. Lopez M, Papaldo P, Di Lauro L, Barduagni M, Perno CF, Barduagni A. Mitomycin C in patients with metastastic breast cancer refractory to hormone therapy and chemotherapy. *Oncology* 1983, **40**, 244–247.
14. Wise GR, Ruhn IN, Godfrey TE. Mitomycin C in large infrequent doses in breast cancer. *Med Pediatr Oncol* 1976, **2**, 55–60.
15. Pasterz RB, Buzdar AU, Hortobagy GN, Blumenschein GR. Mitomycin in metastatic breast cancer refractory to hormonal and combination chemotherapy. *Cancer* 1985, **56**, 2381–2384.
16. *WHO Handbook for Reporting Results of Cancer Treatment.* Geneva, WHO, 1979.
17. Creech RH, Catalana R, Shah MK, Dayal H. A randomized trial of adriamycin vs. mitomycin at low doses in CMF refractory breast cancer patients. *Proc Am Soc Clin Oncol* 1982, **1**, 88.
18. De Lena M, Jirillo A, Villa S *et al.* Preliminary results with adriamycin (A) plus mitomycin (M) combination in metastatic breast cancer. *Proc Am Soc Clin Oncol* 1981, **22**, 435.
19. Friedman MA, Marcus FS, Cassidy MJ *et al.* 5-Fluorouracil + oncovin + adriamycin + mitomycin C (FOAM): an effective program for breast cancer, even for disease refractory to previously chemotherapy. A Northern California Oncology Group (NCOG) study. *Cancer* 1983, **52**, 193–197.
20. Howell A, Morrison JM, Bramwell VHG, Harland R, Moneypenny IJ. Dibromodulcitol, mitomycin C and vinblastine (DMV) chemotherapy in advanced breast cancer. *Eur J Cancer Clin Oncol* 1984, **20**, 873–876.
21. Perez DJ, Powles TJ, Gazet JC, Ford HT, Coombs RC. Mitomycin C, melphalan and methotrexate combination chemotherapy for palliation of disseminated breast cancer. *Cancer Chemother Pharmacol* 1984, **13**, 36–38.
22. Hoogstraten B, George SL, Samax B *et al.* Combination chemotherapy and adriamycin in patients with advanced breast cancer: a Southwest Oncology Group study. *Cancer* 1976, **38**, 13–20.
23. Steiner R, Stewart JF, Cantwell BMJ, Minton MJ, Knight RK, Rubens RD. Adriamycin alone or in combination with vincristine in the treatment of advanced breast cancer. *Eur J Cancer Clin Oncol* 1983, **19**, 1043–1052.
24. Shipp SK, Muss HB, Westrick MA *et al.* Vincristine, doxorubicin, and mitomycin (VAM) in patients with advanced breast cancer previously treated with cyclophosphamide, methotrexate and 5-fluorouracil (CMF): a clinical trial of the Piedmont Oncology Association (POA). *Cancer Chemother Pharmacol* 1983, **11**, 130–133.
25. Borovik R, Epelbaum R, Cohen Y, Robinson E. Mitomycin, doxorubicin and vinblastine as second line chemotherapy in patients with advanced breast cancer. *Cancer Treat Rep* 1986, **70**, 517–518.
26. Di Stefano A, Yap HY, Blumenschein GR. Doxorubicin, mitolactol (dibromodulcitol) and mitomycin C treatment for patients with metastatic breast cancer previously treated with cyclophosphamide and methotrexate, 5-FU, vincristine and prednisone (CMFVP). *Cancer Treat Rep* 1981, **65**, 33–38.
27. Andersson M, Daugaard S, von der Maase M, Mouridsen HT. Doxorubicin versus mitomycin vesus doxorubicin plus mitomycin in advanced breast cancer: a randomized study. *Cancer Treat Rep* 1986, **70**, 1181–1186.

28. Bishop J, Hillcoast B, Raghovan P *et al.* Mitomycin C, mitoxantrone in previously treated patients with advanced breast cancer. *Proc Am Soc Clin Oncol* 1984, **3**, 116.
29. Van Oosterom AT, Smith IE, Muggia FM, Engelsman E, Powles TJ. Refractory breast cancer: phase II study of *n*-AMSA and mitomycin C. *Proc Am Soc Clin Oncol* 1984, **21**, 409.
30. Sledge G, Einhorn L, Williams S, Lochner P. Vindesine and mitomycin +/− methotrexate as second line chemotherapy for metastatic breast cancer. *Proc Am Soc Clin Oncol* 1984, **4**, 59.
31. Garewal HS, Brooks RJ, Jones SE, Miller TP. Treatment of advanced breast cancer with mitomycin C combined with vinblastine or vindesine. *J Clin Oncol* 1983, **1**, 771–775.
32. Denefrio JM, East DR, Troner MB *et al.* Phase II study of mitomycin C and vinblastine in women with advanced breast cancer refractory to standard cytotoxic therapy. *Cancer Treat Rep* 1978, **62**, 2113–2115.
33. Mattsson W, von Eyben F, Hallsten L *et al.* A phase II study of combined 5-fluorouracil and mitomycin-C in advanced breast cancer. *Cancer* 1982, **49**, 217–219.
34. Morgan LR. Adriamycin and mitomycin C in advanced breast cancer. In: Carter SK, Crooke ST, eds. *Mitomycin C: Current Status and New Developments*. New York, Academic Press, 1979, 101–111.
35. Friedman MA. A new combination chemotherapy containing mitomycin C for metastatic breast cancer. In: Carter SK, Crooke ST, eds. *Mitomycin C: Current Status and New Developments*. Orlando, Academic Press, 1979, 113–119.
36. Creech RH, Catalano RB, Shah MK, Dayal H. A phase II study of low dose mitomycin C (MITO) in chemotherapy-refractory metastatic breast cancer patients. *Proc Am Soc Clin Oncol* 1981, **22**, 439.
37. De Lena M, Jitillo A, Brambilla C, Villa S. Mitomycin C in metastatic breast cancer rsistant to hormone therapy and conventional chemotherapy. *Tumori* 1980, **66**, 481–487.
38. Veronesi A, Tirelli V, Galligioni E *et al.* Third-line chemotherapy with mitomycin C, vinblastine and carmustine (BCNU) in refractory breast carcinoma. A pilot study. *Cancer Treat Rep* 1982, **66**, 559–561.
39. Buzdar AU, Legha S, Tashima C. Adriamycin and mitomycin: possible synergistic cardiotoxicity. *Cancer Treat Rep* 1978, **62**, 1005–1008.