Cancer Chemother Pharmacol (1984) 12:1–4

Cancer Chemotherapy and Pharmacology

Original articles

Mitoxantrone: An active new agent in the treatment of advanced breast cancer

Robin C. Stuart-Harris, Thomas Bozek, Nicholas A. Pavlidis, and Ian E. Smith

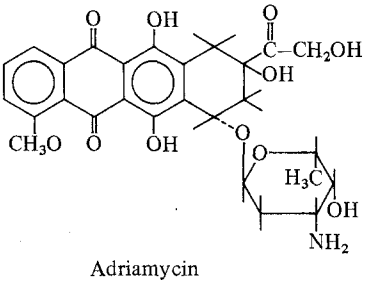
Department of Medicine and Medical Breast Unit, Royal Marsden Hospital, Fulham Road, London SW 3, UK

Summary. *Sixty-five patients with advanced breast carcinoma were treated with mitoxantrone, an anthracenedione with structural similarities to adriamycin. The series included 26 patients who had received no prior chemotherapy. Treatment was given in a dose of 12–14 mg/m² by IV infusion, repeated every 3 weeks. Sixty-two patients were evaluable for response, but all were evaluable for toxicity. One (2%) achieved a complete response and 18 (29%) a partial response (overall response rate 31%). The response rate in patients who had received no prior chemotherapy was 35%, vs 22% in previously treated patients. The median duration of response was 10 months (range 3.5–18.5 months). Two responders had previously failed to respond to adriamycin, and a third responder subsequently failed to respond to adriamycin. Neutropenia was the most frequently seen toxicity, with a WBC of < 2,000/mm³ seen in 26 patients (40%), eight of whom (12%) had a neutropenic infection. Thrombocytopenia (< 100,000/mm³) occurred in 12 patients (18%), but in three of these only after at least 6 months of treatment. Two patients developed readily reversible cardiac failure after prolonged treatment (11–13 months). Other toxicities were in general mild, and the drug was well tolerated: severe alopecia occurred in only one patient. Mitoxantrone is an active well-tolerated agent in the treatment of advanced breast carcinoma, but the risk of neutropenia requires careful supervision. The long-term risk of cardiotoxicity cannot yet be fully assessed.*

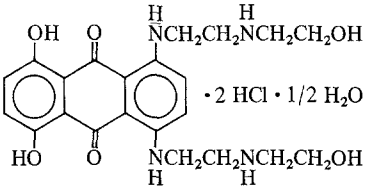
Introduction

Mitoxantrone (dihydroxy-anthracenedione dihydrochloride) is an anthracenedione with structural similarities to adriamycin, but without the amino-sugar moiety at C9 on the parent molecule (Fig. 1). Interest in mitoxantrone developed when it was demonstrated in several experimental tumour systems that the compound had equal or superior activity to adriamycin [5, 6, 8, 14, 26, 30, 31] but with diminished or absent cardiotoxicity [5, 12, 17]. Activity has also been shown against four human breast carcinoma xenografts [2].

Phase-I clinical trials demonstrated that the dose-limiting toxicity was leucopenia [1, 7, 9, 10, 18, 20, 22–25, 28]. On the basis of this information, we started a phase-II single-agent study in November 1980 in the treatment of advanced breast carcinoma and other solid tumours, using a dose of 12–14 mg/m² once every 3 weeks. Our preliminary data indicated useful clinical activity against advanced breast cancer [19], and other studies have since confirmed these findings [15, 29].



Adriamycin



Mitoxantrone

Fig. 1. Chemical structures of adriamycin and mitoxantrone

This report updates our earlier findings in a larger series of patients with advanced breast cancer, and includes long-term follow-up information on both efficacy and toxicity.

Patients and methods

Patients. Between November 1980 and September 1982, 65 patients with histologically proven advanced breast cancer were entered into the study after giving informed consent. Twenty-nine of these patients have been described previously [19]. The median age was 53 years (range 25–76 years). Forty-four were postmenopausal, 12 premenopausal, and eight perimenopausal (less than 2 years from last menstrual period); one was male. Twenty-six had received no prior chemotherapy, and 14 had received only adjuvant chemotherapy.

Dose and schedule. Twenty-six patients were treated with a dose of 12 mg/m² repeated every 3 weeks. In six non-responding patients this was increased to 14 mg/m² after two courses. The remaining 39 patients received 14 mg/m² from the outset. The dose was reduced if WBC nadir was less than

Reprint requests should be addressed to I. E. Smith

1,500/mm^3 or platelet nadir less than 100,000/mm^3. Treatment was given as an IV infusion in 100 ml 5% dextrose over 30 min.

Investigations. Routine investigations for assessment and toxicity were carried out at 3-weekly intervals, as described previously [19]. In addition, nadir blood counts were available for the majority of patients.

Criteria for assessment of response and toxicity. Patients who received a minimum of two courses of therapy or who showed clear evidence of disease progression after one course were considered evaluable for response. Response was defined according to the standard UICC criteria [11]. All patients, whether completing two courses or not, were assessed for toxicity, using WHO recommendations [27].

Results

Response

Sixty-two patients were evaluable for response. The remaining three failed to complete two courses of treatment. One patient achieved a complete response (2%) and 18 a partial response (29%). The overall objective response rate was therefore 19 of 62 (31%).

Response related to prior chemotherapy

In patients who had received no prior chemotherapy nine of 26 (35%) achieved a response, whilst five of 13 (38%) who had received only adjuvant chemotherapy also achieved a response. Of 23 patients who had received prior chemotherapy for advanced disease five (22%) achieved a response.

Response related to site of disease

Response were seen in all major sites of disease involvement except lung. Details are given in Table 1.

Time to achieve response

Response was achieved within 3 weeks in eight patients, 6 weeks in four patients, 9 weeks in five patients, 12 weeks in one patient, and a full 15 weeks in one patient. The mean time to achieve response was 6 weeks.

Response duration

The median duration of response (life-table analysis) was 10 months (range 3.5–18.5 months) (Fig. 2).

Response in adriamycin-treated patients

Details of patients treated sequentially with mitoxantrone and adriamycin are given in Table 2. Of 18 patients who responded to adriamycin, three also responded to mitoxantrone, and three of nine patients who failed to respond to adriamycin responded to mitoxantrone. Of these, two had received adriamycin before mitoxantrone, and the other after mitoxantrone.

Haematological toxicity

The main toxicity was myelosuppression and this was dose-limiting. All patients had a fall in peripheral white blood count during treatment, but usually this was minor and transient with the nadir between 7 and 14 days after treatment. WBC fell to $< 2{,}000/mm^3$ during 44 courses and to $< 1{,}000/mm^3$ during six courses in a total of 26 patients (details in Table 3). There were eight episodes of neutropenic infection; three occurred after the first course, two after the second course, one after the eleventh course, one after the fourteenth course, and one after the fifteenth course of therapy. Seven were successfully treated with antibiotics, but one proved fatal in a patient who refused hospital admission for antibiotic treatment. There was no significant difference in mean WBC nadir for patients treated with 12 mg/m^2 or 14 mg/m^2 (2,800/mm^3 vs 2,900/mm^3), although six patients treated at the higher dose were self-selecting in that they had shown no haematological toxicity to initial therapy at the lower dose.

Thrombocytopenia of $< 100{,}000/mm^3$ occurred in 12 patients during 19 cycles. Three of these, all with liver metastases, developed prolonged thrombocytopenia after more than 6 months of therapy and required cessation of treatment. Each had elevation of liver enzymes, but only marginal elevation of serum bilirubin at the start of therapy. Only one had had prior chemotherapy. Bone marrow aspiration was performed in two and was normal in both.

Table 1. Response related to site of disease

	No. of patients	Responses
Soft tissue	39	13 (33%)
Lymph nodes	17	6 (35%)
Lung	19	0 –
Pleura	6	3 (50%)
Bone	15	5 (33%)
Liver	21	7 (33%)

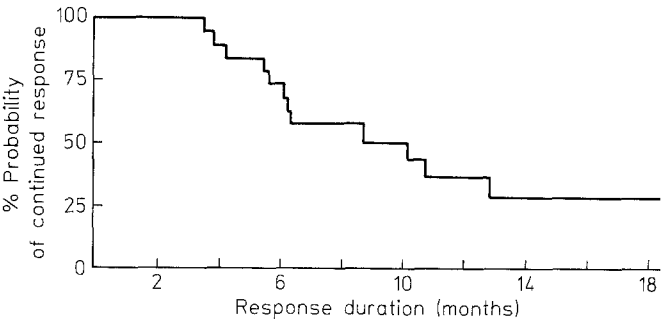


Fig. 2. Response duration of patients responding to mitoxantrone (life-table analysis)

Table 2. Response related to adriamycin

	No. of patients	Response to mitoxantrone
Adriamycin responders	18	3[a]
Adriamiycin non-responders	9	3[b]
Adriamycin adjuvant therapy	6	1
Adriamycin not given	29	12

[a] All received adriamycin before mitoxantrone

[b] Two received adriamycin before mitoxantrone, one after mitoxantrone

Table 3. WBC nadirs during treatment with mitoxantrone

Dose	No. of patients	Courses	$> 3{,}000/mm^3$	$2{,}000-3{,}000/mm^3$	$1{,}000-1{,}900/mm^3$	$< 1{,}000/mm^3$	Mean nadir ($\times 10^3/mm^3$)
14 mg/m^2	44	127	44	56	24	3	2.9
12 mg/m^2	34	74	27	24	20	3	2.8

Table 4. Non-haematological toxicity in 65 patients

	No. of patients	Percentage
Nausea	17	26
Vomiting	20	31
Mild hair loss[a]	35	60
Alopecia requiring wig	1	2
Stomatitis	12	18
Dry mouth	15	23
Malaise	16	25
Diarrhoea	5	8
Paraesthesiae	5	8
Nail dystrophy	4	6
Dizziness	3	5
Transient loss of taste	2	3

[a] Seven patients inevaluable due to pre-existing alopecia

Cardiotoxicity

Four patients received 175 mg/m^2 or more, and two of these developed cardiac failure, the first after a total dose of 340 mg (243 mg/m^2) over 13 months and the second after 296 mg (175 mg/m^2) over 11 months. In both patients endomyocardial biopsy showed dilatation of the myocardium, hypertrophy of muscle fibres, and increased interstitial fibrosis. Both patients responded to standard diuretic therapy. Neither had received prior adriamycin, although one had received prior mediastinal irradiation. The two remaining patients who had received more than 175 mg/m^2 developed significant falls in ventricular ejection fraction [3], as measured by 99M Tc ECG gated blood pool cardiac scans, but without clinical features of cardiac failure. These patients had received 253 mg/m^2 and 217 mg/m^2, respectively. Neither had received prior adriamycin or mediastinal irradiation. Endomyocardial biopsy was carried out in the patient who had received 253 mg/m^2 and showed similar features to the biopsies described above. Endomyocardial biopsy was obtained in one further patient who showed a significant fall in ventricular ejection fraction after only 47 mg/m^2. This patient had received 313 mg/m^2 of adriamycin previously, but no mediastinal irradiation. The biopsy showed only minimal evidence of hypertrophy and dilatation. The occurrence of cardiotoxicity and the histological changes observed will be the subject of a further, separate report.

Other toxicities

Details of other toxicities are given in Table 4. In general the drug was well tolerated in the great majority of patients, and several commented on its lack of side-effects compared with previous chemotherapy. Vomiting occurred during treatment in 31% of patients, but this was usually mild and of short duration. Only one patient (2%) had alopecia severe enough to require a wig, although limited hair loss was reported in 60% of patients. Several patients with adriamycin-induced alopecia had hair regrowth during mitoxantrone treatment.

Discussion

The response rate achieved here for mitoxantrone in the treatment of advanced breast cancer appears to be as high as for most other single agents apart perhaps from adriamycin; indeed, several conventional drugs currently used in first-line combination therapy have a lower response rate [4, 13]. Likewise, the median duration of response of 10 months is as good as that reported for several combination chemotherapy regimens, and longer than that for most other single agents [4]. It is likely that these results were influenced to some extent by treating relatively fit patients who had received no previous chemotherapy; however, it should be noted that responses were seen in all groups of patients whether previously treated with cytotoxic drugs or not.

In view of structural similarities, it is appropriate to compare mitoxantrone with adriamycin. It was of interest that complete cross resistance between these drugs does not appear to exist. Two patients who failed to respond to adriamycin subsequently responded to mitoxantrone, and a third mitoxantrone responder subsequently failed to respond to adriamycin. Responses to mitoxantrone in adriamycin-resistant patients have also been reported by others [15, 29]. A further striking difference between the two agents was the absence, except in one patient, of severe alopecia with mitoxantrone.

Experimental studies of mitoxantrone initially suggested absence of cardiotoxicity when it was compared with adriamycin in beagle dogs [12, 17], and diminished cardiotoxicity in rats [5]. Two patients in this study developed cardiac failure after prolonged treatment, but in both this was readily reversible with standard treatment and endomyocardial biopsies did not show severe features of anthracycline cardiomyopathy. Two further patients showed physiological but not clinical cardiac impairment, with similar histological features on biopsy. Reversible cardiac failure has also been noted in one study, albeit after adriamycin therapy [16], but not in two others [15, 21]. Further clinical experience is required to determine the significance and severity of this problem. On the basis of our current experience we recommend caution with prolonged use of mitoxantrone to a total dose of 175 mg/m^2 or more. Caution is also required at much lower doses in adriamycin-pretreated patients.

The short-term dose-limiting toxicity is neutropenia. This was severe only in a small minority of patients, but the fact that occasional septicaemic episodes were seen again urges for caution, particularly when patients are treated on an out-patient basis. Thrombocytopenia was not a problem except perhaps after long-term usage, and further clinical information is required to assess this risk more fully. Apart from this, a notable feature of the drug was its low incidence of unpleasant

side-effects, and most patients tolerated treatment very well. This, in association with its anti-tumour activity, justifies further use of this drug in the treatment of advanced breast cancer. In particular, experience is now needed in the use of mitoxantrone in combination with other agents.

Acknowledgement. We would like to thank Mrs Lorna Carr for preparing this manuscript.

References

1. Alberts DS, Griffiths KS, Goodman GE, Herman TS, Murray E (1980) Phase I clinical trial of mitoxantrone: a new anthracenedione anticancer drug. Cancer Chemother Pharmacol 5: 11–15
2. Bailey M, Raghaven D, Shorthouse M (1980) The response to chemotherapy of human breast tumour xenografts. Proc Am Assoc Cancer Res 21: 265
3. Borer JS, Bacharac SL, Green MV, Kent KM, Johnson GS, Epstein SL (1978) The effect of nitroglycerine on exercise-induced abnormalities of L.V. regional function and ejection fraction in C.A.D. Circulation 57: 314–320
4. Carter SK (1967) Integration of chemotherapy into combined-modality treatment of solid tumours. VII. Adenocarcinoma of the breast. Cancer Treat Rev 3: 141–174
5. Cheng CC, Zbinden G, Zee-Cheng RKY (1979) Comparison of anti-neoplastic activity of amino-ethylamino anthraquinones and anthracycline antibiotics. J Pharm Sci 68: 393–396
6. Corbett TH, Roberts BJ, Trader MW, Laster WR, Griswold DP, Schabel FM (1982) Response of transplantable tumors of mice to anthracenedione derivatives alone and in combination with clinically useful agents. Cancer Treat Rep 66: 1187–1200
7. Estey EH, Keating MJ, McCredie KB, Bodey GP, Freireich EJ (1981) Phase I–II study of dihydroxyanthracenedione (DHAD) in acute leukemia. Proc Am Assoc Cancer Res 22: 490
8. Fujimoto S, Ogawa M (1982) Antitumor activity of mitoxantrone against murine experimental tumors: comparative analysis against various antitumor antibiotics. Cancer Chemother Pharmacol 8: 157–162
9. Goldsmith MA, Ohnuma T, Roboz J, Jaffrey I, Greenspan EM, Holland JF (1981) Phase I clinical and pharmacological evaluation of mitoxantrone. Proc Am Assoc Cancer Res 22: 388
10. Hagenberg L, Loynds P, Nagel GA (1980) 2-/hydroxyethyl/amino-ethyl/amino 9.10 anthrazendione dihydrochloride/NSC 301739 – ein neues Zytostaticum. Onkologie 3: 322–324
11. Hayward JL, Rubens RD, Carbone PP, Heuson J-C, Kumaoka S, Segaloff A (1977) Assessment of response to therapy in advanced breast cancer. Br J Cancer 35: 292–298
12. Henderson BM, Dougherty WJ, James VC, Tilley LP, Noble JF (1982) Safety assessment of a new anti-cancer compound, mitoxantrone, in beagle dogs compared with doxorubicin. I. Clinical observations. Cancer Treat Rep 66: 1139–1143
13. Hoogstraten B, Fabian C (1979) A reappraisal of single drugs in advanced breast cancer. Cancer Clin Trials 2: 101–109
14. Johnson RK, Zee-Cheng RKY, Lee WE, Acton EM, Henry DW, Cheng CC (1979) Experimental antitumor activity of amino-anthraquinones. Cancer Treat Rep 63: 425–439
15. Neidhart JA, Roach RW (1982) A randomized study of mitoxantrone and adriamycin in breast cancer patients failing primary therapy. Proc Am Soc Clin Oncol 1: 86
16. Schell FC, Yap HY, Blumenschein G, Valdivieso M, Bodey G (1982) Potential cardiotoxicity with mitoxantrone. Cancer Treat Rep 66: 1641–1643
17. Sparano BM, Gordon G, Hall C, Iatropoulos MJ, Noble JF (1982) Safety assessment of a new anticancer compound, mitoxantrone, in beagle dogs: comparison with doxorubicin. II. Histologic and ultrastructural pathology. Cancer Treat Rep 66: 1145–1158
18. Stewart JA, McCormack JJ, Krakoff IH (1982) Clinical and clinical pharmacologic studies of mitoxantrone. Cancer Treat Rep 66: 1327–1331
19. Stuart-Harris RC, Smith IE (1982) Mitoxantrone: a phase II study in the treatment of patients with advanced breast carcinoma and other solid tumours. Cancer Chemother Pharmacol 8: 179–182
20. Ungerleider RS, Cohen LF, Glaubiger DL et al. (1981) Dihydroxyanthracenedione/NSC 301739, mitoxantrone, phase I evaluation in children. Proc Am Assoc Cancer Res 22: 392
21. Unverferth DU, Balcerzak SP, Neidhart JA (1982) Cardiac evaluation of aclacinomycin and dihydroxyanthracenedione. Proc Am Assoc Cancer Res 23: 135
22. Valdivieso M, Bedikian AY, Burgess MA, Savaras N, Jeffers WB, Bodey GP (1981) Phase I clinical study of dihydroxyanthracenedione administered on a 5 day i.v. schedule. Cancer Treat Rep 65: 841–844
23. Van Echo DA, Whitacre NY, Aisner J, Wiernik PH (1981) Phase I trial of dihydroxyanthracenedione. Cancer Treat Rep 65: 831–834
24. Vietti T, Nix W, Kim T, Cappiello V (1981) Dianhydroanthracenedione in children with advanced malignant disease – a POG and American Cyanamid phase I study. Proc Am Assoc Cancer Res 22: 237
25. Von Hoff DD, Pollard E, Kuhn J, Murray E, Coltman CA (1980) Phase I clinical investigation of 1,4-dihydroxy-5,8-bis(((2-)(2-hydroxyethyl)amino(ethyl)amino))-9,10-anthracenedione dihydrochloride (NSC 301739), a new anthracenedione. Cancer Res 40: 1516–1518
26. Wallace RE, Murdock KC, Angier RB, Durr FE (1979) Activity of a novel anthracenedione, 1,4-dihydroxy-5,8-bis(((2-)(2-hydroxyethyl)amino(ethyl)amino))-9,10-anthracenedione dihydrochloride against experimental tumors in mice. Cancer Res 39: 1570–1574
27. World Health Organization (1979) WHO handbook for reporting results of cancer treatment. WHO, Geneva (Offset publication no. 48)
28. Wynert WR, Harvey HA, Lipton A, Schweitzer J, White DS (1982) Phase I study of a 5-day schedule of mitoxantrone. Cancer Treat Rep 66: 1303–1306
29. Yap HY, Blumenschein GR, Schell FC, Buzdar AU, Valdivieso M, Bodey GP (1981) Dihydroxyanthracenedione: a promising new drug in the treatment of metastatic breast cancer. Ann Intern Med 95: 694–697
30. Zee-Cheng RKY, Cheng CC (1978) Antineoplastic agents. Structure-activity relationship study of bis/substituted aminoalkylamino/anthraquinones. J Med Chem 21: 291–294
31. Zee-Cheng RKY, Podrebarac EG, Menon CS, Cheng CC (1979) Structural modification study of bis/substituted aminoalkylamino/anthraquinones. An evaluation of the relationship of the (2-)(2-hydroxyethyl)amino(ethyl)amino side chain with antineoplastic activity. J Med Chem 22: 501–505

Received June 27, 1983/Accepted September 13, 1983