Cancer Chemother Pharmacol (1991) 28: 402–404
034457049100124Z

Cancer Chemotherapy and Pharmacology

Short communication

Mitozantrone and prednimustine in the treatment of advanced breast cancer – a toxic regimen with low activity

M. E. R. O'Brien[1], D. M. Eccles[1], S. G. Allen[1], G. Knight[2], A. Rodger[1], U. Chetty[3] J. F. Smyth[1], and R. C. F. Leonard[1]

[1] Imperial Cancer Research Fund Medical Oncology Unit and Radiation Oncology Unit, University Department of Clinical Oncology, Western General Hospital, Edinburgh, [2] Scottish Cancer Trials Office, [3] University Department of Clinical Surgery, Longmore Hospital, Edinburgh, Scotland, UK

Received 2 October 1990/Accepted 22 April 1991

Summary. The combination of mitozantrone and prednimustine has been reported to elicit response rates of around 50% in patients with advanced breast cancer. In the present trial, either three or nine courses of this combination were given to previously untreated patients with advanced breast cancer. Mitozantrone was given at 12 mg/m^2 on day 1 and prednimustine was given orally at 130 mg/m^2 on days 1–5; treatment was repeated every 4 weeks. A total of 34 patients were treated; the performance status was 0–1 in 29 subjects and 2 in 5 cases. Locoregional disease only was present in 13 patients; 9 showed lung involvement; 8, liver; 3, bone; and 1, stomach involvement. A total of 10 subjects had received no prior hormone therapy. The median disease-free interval from the time of initial diagnosis was 24 months (range, 0–144 months). In all 14/23 patients exhibited an oestrogen receptor level of >20 fmol. Grade 1 nausea and vomiting occurred in 16 patients and that of grade 2–3, in 11 subjects; nausea was prolonged for >10 days in 7 cases. Grade 4 neutropenia occurred in 2 patients. The response rate was 21% (95% confidence interval, 8%–38%). The combination of mitozantrone and oral prednimustine is toxic and displays low activity.

Introduction

Prednimustine is an oral ester of chlorambucil and prednisolone that has shown activity in several types of human cancer, notably lymphoma, breast and ovarian carcinoma [3, 4, 6–8]. Three phase II studies using prednimustine as a single agent in advanced breast cancer have reported modest toxicity and varying activity of 9%, 0 and 40% [2, 10, 12]. Two large phase II studies using a combination of mitozantrone and prednimustine have achieved response rates of around 50% with responses being observed at all sites of disease [1, 11, 13]. The present study was a randomised phase II trial using these two agents in which patients were randomised to either three or nine courses of prednimustine and mitozantrone. Unfortunately, the reported response rate was not reproducible and the randomised study was therefore abandoned.

Patients and methods

Patients exhibiting advanced breast cancer who had not previously undergone chemotherapy (apart from adjuvant chemotherapy) and displayed a good performance status and a life expectancy of at least 3 months were entered into the study. The patients characteristics are shown in Table 1. Prednimustine was given orally at a dose of 130 mg/m^2 on days 1–5, and mitozantrone was given i.v. at 12 mg/m^2 on day 1. Treatment was repeated at 28-day intervals. Patients who had been randomised to receive three courses stopped treatment at that point, and those who had been randomised to nine courses continued treatment until either their disease had progressed, toxicity had become limiting or all nine courses had been completed. The blood count was checked before each course and treatment was delayed by 1 week if the WCC was $<3\times10^9$/l or the platelet count was $<100\times10^9$/l. If the WCC was $2.5-3\times10^9$/l or the platelet count was $75-100\times10^9$/l after a 1-week delay, the dose was reduced to 75% of the starting level. Objective response was assessed after three courses using the criteria of the International Union Against Cancer [5].

Results

A total of 34 patients were entered into the study. The median age was 58 years (range, 34–73 years). The performance status was 0–1 in 29 patients and 2 in 5 cases. Locoregional disease only was present in 13 subjects; 9 showed lung involvement; 8, liver; 3, bone; and 1, stomach involvement. Ten patients had received no prior hormone therapy. The median disease-free interval from the time of initial diagnosis was 24 months (range, 0–144 months). In all, 14/23 subjects displayed an oestrogen receptor level of >20 fmol.

All 34 patients were assessable for toxicity and response. In all, 2 of the 5 subjects whose disease progressed

Offprint requests to: R. C. F. Leonard

Table 1. Patients' characteristics

Median age at entry		58.5 (34–73) years
Disease-free interval:		
	0	7
	<24 months	9
	24–48 months	7
	>48 months	11
Menopausal status:		
	Premenopausal	5
	Postmenopausal	28
	Perimenopausal	1
Number of previous hormone treatments:		
	0	10
	1	8
	2	8
	3	7
	4	1
Oestrogen receptor values:		
	Unknown	11
	<20	9
	20–50	2
	50–100	6
	>100	6
Performance status:		
	0	13
	1	16
	2	5
Sites of disease:		
	Locoregional	13
	Bone + locoregional	3
	Bone + lung/lung	9
	Liver + bone	8
	Stomach +	1
Stage:		
	I + II	18
	III + IV	11
	Unknown/Paget's/bilateral	5
Adjuvant treatment:		
	Tamoxifen	7
	Oophorectomy	2
	Chemotherapy	0
	None	25

after 1 course died; of the remaining patients, 4 received 2 courses and 18 finished 3. Of the 18 subjects who completed 3 courses, 7 had been randomised to receive 9 courses on the longer-duration arm of the trial; however, only 3 of the latter received 4 courses, 3 finished 5 and 1 completed the intended 9 courses. In 2 cases, treatment was stopped after 3 and 4 courses respectively, due to toxicity. The responses observed included four in soft tissue (one complete response and three partial responses), two partial responses in the lung and one in the stomach. In all, 12 patients exhibited stable disease and 15 developed progressive disease. The response rate was 21% (95% confidence interval, 8%–38%).

Table 2 shows WHO toxicity grading for nausea and vomiting, alopecia, cardiac toxicity, neurotoxicity and constipation [9]. The number of days during which patients felt nauseated was recorded in 32/34 cases. One subject exhibited nausea as a prominent symptom prior to chemotherapy and was therefore not evaluable for this toxicity; one patient died before toxicity was assessed. For the remaining 30 patients, the longest duration of nausea in any one cycle was reported: only 6 subjects did not experience nausea on any occassion; 8 individuals experienced nausea for ≤ 3 days; 9 patients, for 5–7 days; 3 subjects, for 10–14 days; and 4 patients, for 21–30 days. Two subjects developed life-threatening neutropenia with associated infections, and one patient developed grade 3 cardiotoxicity with symptomatic dysfunction that required treatment with digoxin and vasodilators. Toxicity contributed to discontinuation of treatment in four patients who could have continued therapy to finish the protocol. In five cases, treatment was delayed on one occasion due to neutropenia, and in one case a 2-week delay and a dose reduction to 75% of the starting level was required.

Table 2. Toxicity of the present regimen

	WHO grade				
	0	1	2	3	4
Nausea and vomiting	7	16	7	4	0
Hair loss	18	11	5	0	0
Cardiac	3	0	2	1	0
Neurotoxicity	3	3	0	0	0
Constipation	3	4	0	0	0
Neutropenia	18	7	7	0	2
Thrombocytopenia	33	1	0	0	0

Discussion

The present study attempted to answer the question as to the optimal duration of chemotherapy in patients with advanced breast cancer who had been randomised to three vs nine courses. Unfortunately, the response rate reported for the present treatment regimen could not be reproduced; therefore, the randomisation and trial were abandoned. It is not clear why our response rate was so inferior to that reported in the NOSTE trial [13]. All patients who entered our trial had not previously been treated, showed a good performance status and exhibited disease that was compatible with that found in the groups of patients investigated by Schmid and Manegold [13], Bodenstein et al. [1] and Preiss et al. [11]. The study by Schmid and Manegold [13] reported on 94 evaluable patients who achieved a response rate of about 51%, 12% of whom had previously been treated, and responses were observed at all sites of disease. The scheduling used differed slightly from that chosen for the present study, with prednimustine being given at a lower dose of 100 mg/m^2 but on days 3–7 (vs days 1–5 in the present study). However, the studies by Bodenstein et al. [1] and Preiss et al. [11] used the same schedule applied in the present study and reported a response rate of 50% in 60 previously untreated patients. It is therefore unlikely that scheduling or patient selection would account for the discrepancy in response rates.

In addition to its low activity, the present regimen produced considerable toxicity. Grade 3 nausea and vomiting

occurred in 4 patients and 16 subjects experienced nausea. Generally the parameter nausea is subsumed in the grade 1 toxicity category of *nausea and vomiting*, and the duration of this disabling symptom is not accounted for in the toxicity grading. This particular drug combination produced nausea that lasted for >10 days in 7 patients.

As the treatment of advanced breast cancer is based on symptom control, it was considered unethical to continue offering these patients a regimen that exhibited such poor activity; thus, the trial was discontinued. A separate grading system for nausea is needed for the assessment of new drugs and drug combinations, as this toxicity significantly interferes with the quality of life of cancer patients.

References

1. Bodenstein H, Preiss J, Hilfrich J, Kamin K, Corterier H, Hohlweg-Majert P, Bothmann GA, Rauschecker H (1987) Treatment of metastatic breast cancer with Novantrone and Sterecyt – an efficient therapy with low subjective toxicity. Proceedings of a Satellite Symposium, Hamburg, September, pp 53–58
2. EORTC Clinical Screening Cooperative Group (1977) A phase II clinical trial of prednimustine. Biomedica 27: 158–161
3. Harrap KR, Riches PG, Gilbety ED, Sellwood SM, Wilkinson R, Konyves I (1977) Studies on the toxicity and antitumour activity of prednimustine, a prednisolone ester of chlorambucil. Eur J Cancer 13: 873
4. Hartley-Asp B, Gunnarsson PO, Liljekvist J (1986) Cytotoxicity and metabolism of prednimustine, chlorambucil and prednisolone in a Chinese hamster cell line. Cancer Chemother Pharmacol 16: 85–90
5. Hayward JL, Carbone PP, Heuson JC, Kumaoka S, Segaloff A, Rubens RD (1977) Assessment of response to therapy in advanced breast cancer. Eur J Cancer 13: 89–94
6. Idestrom J, Kimby E, Bjorkjolm M (1982) Treatment of chronic lymphocytic leukaemia and well-differentiated lymphatic lymphoma with continuous low- or intermittent high-dose prednimustine versus chlorambucil/prednisolone. Eur J Cancer Clin Oncol 18: 1117–1121
7. Johnsson JE, Trope C, Mattson W, Grundsoll HH, Aspergreen K, Konyves I (1979) Phase II study of LEO 1031 (prednimustine) in advanced ovarian carcinoma. Cancer Treat Rep 63: 421–424
8. Lober J, Mouridsen HT, Christiansen IE, Dombernovsky P, Mattson W, Rorth M (1983) A phase three trial comparing prednimustine (Leo 1031) and chlorambucil plus prednisolone in advanced breast cancer. Cancer 52: 1570
9. Miller AB, Hoogstraten B, Staguet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 56: 2740
10. Mouridsen HT, Kristensen D, Nielsen J, Dombernowsky P (1980) Phase II trial of prednimustine, L-1031 (NSC-134087) in advanced breast cancer. Cancer 46: 253–255
11. Preiss J, Hilfrich J, Corterier H, Rauschecker H, Hohlweg-Majert P, Bodenstein H (1987) Novantrone and Stereocyt in metastatic breast cancer: a multicenter study with first- and second-line therapy. ECCO 4. Proceedings 4th European Conference on Clinical Oncology and Cancer Nursing, Madrid, 1–4 November, p 130
12. Rankin EM, Harvey C, Knight RK, Rubens RD (1987) Phase II trial of prednimustine as first-line chemotherapy in patients with advanced breast cancer. Cancer Treatment Rep 72 (11): 1107–1108
13. Schmid H, Manegold C (1988) Phase II study of mitoxantrone/prednimustine (NOSTE) in advanced breast cancer. Proc Am Soc Clin Oncol 7: A135