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Weekly Doxorubicin With or Without High-dose Medroxyprogesterone Acetate in Hormone-resistant Advanced Breast Cancer. A Randomised Study

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For the Norwegian Breast Cancer Group

In a randomised study, 218 patients with advanced breast cancer, resistant to hormone therapy, received either doxorubicin 20 mg every week (Awkly) alone or Awkly combined with high doses (1000 mg daily) of oral medroxyprogesterone acetate (HD-MPA). Of the 210 evaluable patients, the response rates were 26% [95% confidence interval (CI) 18–34%] for Awkly and 38% (95% CI 29–47%) for Awkly + HD-MPA ($P = 0.08$). There was no significant difference with regard to duration of response. Median survival was 11 months in both groups. Considerable toxicity was seen from HD-MPA, particularly weight gain and fluid retention. The present study provides evidence that, in concordance with preclinical studies and a previous randomised study, interaction between chemotherapy and HD-MPA may exist in breast cancer normally resistant to hormone therapy. For further studies, other gestagens and/or a dose reduction could be investigated.

Key words: advanced breast cancer, doxorubicin, hormone resistant, medroxyprogesterone acetate.
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INTRODUCTION

IN EXPERIMENTAL studies reported by Formelli and colleagues [1] sublines of the 13 762 mammary adenocarcinoma were identified which differed in sensitivity to medroxyprogesterone acetate (MPA). MPA was found to be active on sublines sensitive to 17-β-oestradiol, but it also improved the activity of doxorubicin on hormone-insensitive sublines. Subsequently, another group [2] reported increased responses to methotrexate and vincristine after pretreatment with MPA, independent of its growth-inhibitory action, confirming a previous clinical study [3]. When cultured human breast cancer cells (MCF-7) were exposed to MPA prior to treatment with doxorubicin [4], enhancement of the cytotoxic drug on cell yield, after further growth of viable cells, was observed. Notably, when cells resistant to the growth-inhibitory action of MPA were examined, MPA/doxorubicin synergism could still be demonstrated. The authors concluded that the effects of doxorubicin, like those of methotrexate and vincristine, could be enhanced by pretreatment with MPA, confirming the data of Formelli's group.

We have previously reported [5] on a randomised study of chemotherapy alone versus chemotherapy combined with high-dose MPA (HD-MPA) among patients with advanced breast cancer with oestrogen receptor (ER)-negative tumour tissue. That study was undertaken to analyse the contribution of HD-MPA in combination with chemotherapy, when given to patients that normally would be anticipated not to respond to MPA alone. We found a higher response rate for the combined treatment group. This could be interpreted as confirmative of the experimental data. However, the higher response rate could still theoretically be explained by endocrine sensitivity, since some patients had tumours with progesterone receptors, or they could have responded via a mechanism mediated by androgen receptors or other hitherto unknown mechanisms.

In order to further analyse the possibility of a true interaction (as opposed to an additive effect) between chemotherapy and HD-MPA, patients with disease manifestations proven to be resistant to endocrine therapy were selected, analogous to the experimental situation where cell lines were tested and found insensitive to MPA.

PATIENTS AND METHODS

Three centres randomised patients. There was one random numbers table located at the study centre in Oslo, and the majority (75%) of patients were randomised there. No attempt has been made to analyse therapeutic outcome by centre.

For this study, patients who were indisputably, as far as was practically possible, resistant to hormone therapy were recruited. This part of the protocol was, therefore, rather meticulously outlined and endocrine resistence was defined as:

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1. Progression without initial response on two different hormone regimens among patients with ER-positive and ER-unknown tumour tissue.
2. Progression on one endocrine treatment, usually anti-oestrogen, among ER unknown, where the clinical situation would demand chemotherapy, e.g. in a young patient with clearly progressing liver metastases.
3. Progression on three different endocrine treatments after initial response to one of them.
4. Progression on more than three endocrine manoeuvres if the patient has responded to more than one of these.
5. Duration of endocrine therapy should be at least 3 months (but some clinical judgement must be applied).

Receptor status was measured in two laboratories as reported previously [5].

Patients should not have received chemotherapy for advanced disease, while adjuvant hormone- or chemotherapy, albeit not with anthracyclines, was allowed.

Patients should have performance status ≤ 2. A pretreatment initial white cell count (WCC) of $\geq 4 \times 10^9$/l and platelet (plt) count of $\geq 125 \times 10^9$/l were required. Patients with another type of neoplasm, or other medical conditions which could preclude adherence to the treatment or assessment schedule, were excluded. Metastases were measurable or evaluable. Patients with brain metastases, leptomeningeal involvement or osteoblastic lesions as the only manifestation of the disease were excluded.

Prior to initial treatment, all patients underwent physical examination. Blood count, chest X-rays, bone isotope scans and/or bone survey radiographs and measurements of indicator lesions, whenever possible, were obtained. If indicated by liver function tests, liver scan, ultrasound sonography or computer tomography (CT) were performed. Brain scans and/or CT were performed in those patients who had symptoms or signs suggestive of central nervous system metastases.

Patients were allocated by random numbers on to one of two treatment regimens:

(1) Doxorubicin, given as a 5–10-min infusion, 20 mg every week to a total maximum of 750 mg/m^2 (Awkly); (2) Awkly combined with MPA, 500 mg orally twice daily from start of and as long as Awkly was given.

Ongoing endocrine therapy was stopped. There was no wash out time.

Blood counts were performed every 4–5 weeks, but nadir values were not determined.

Second-line chemotherapy was 5-fluorouracil 1000 mg/m^2 days 1 and 2 and mitomycin-C 6 mg/m^2 day 2 (FuMi) [5].

Main patients' characteristics are summarised in Tables 1 and 2. There were no significant differences between the two groups with regard to important prognostic factors. Time from previous adjuvant chemotherapy was not recorded.

Tumour assessments were made at 8 weeks and thereafter every 3 months. Liver metastases were evaluated by ultrasound and/or CT scan, whichever was suitable in each case. Skeletal metastases were evaluated by X-ray, alkaline phosphatase levels and patient's record of pain. A partial response was recorded when there was sclerosis in lytic metastases, reduction in alkaline phosphatase (if suitable) and pain. A complete response was recorded when there was normalisation of osteolytic metastases, alkaline phosphatase (if suitable) and alleviation of pain.

In general, the criteria used for evaluation were those recommended by UICC [6]. The duration of no change was taken to be 8 weeks or more.

Table 1. Main patients' characteristics

	Doxorubicin (n = 111)	Doxorubicin + HD-MPA (n = 107)
Mean age, years	56	57
Premenopausal	30	24
Postmenopausal	81	83
Oestrogen receptor (pmol/g)		
0	18	18
1–5	9	7
6–9	3	2
≥10	18	22
Unknown	63	58
Disease-free interval (months)		
Median	23	20
Range	(1–267)	(1–253)
Time from first metastases until randomisation (months)		
Median	12	9
Range	(1–142)	(1–129)

Table 2. Dominant site of metastases (all patients)

	Doxorubicin n = 111		Doxorubicin + HD-MPA n = 107	
	%	%	%	%
Skeletal	61	55	56	52
Soft tissue	43	39	42	39
Visceral	7	6	9	8

Statistical methods

The comparability of the two teatment groups with respect to baseline variables was assessed by performing a χ^2 test for categorical variables and a two-sample Student's t-test for means. Survival curves were calculated by the Kaplan–Meier table method, and significance testing as performed by the log-rank method [7].

RESULTS

A total of 218 patients with advanced breast cancer were randomised during the period of January 1987 to September 1990. 8 patients (5 Awkly, 3 Awkly+MPA) were excluded since they did not have evaluable disease (e.g. sclerotic skeletal metastases only). Thus, 210 evaluable patients with hormone-resistant disease, as defined above, remained.

106 patients were in the Awkly alone group and 104 in the combined treatment group. The response rates were 28/106 [26%, 95% confidence interval (CI) 18–34%] for Awkly versus 39/104 (38%, 95% CI 29–47%) (P = 0.08) for Awkly+HD-MPA (Table 3). The median durations of response were 9 (range 3–30) months in the Awkly group versus 8 (range 2–48) months in the combined group.

22 patients died before eight cycles of chemotherapy had been given. They were considered to have died from cancer and, therefore, to have had progressive disease. 13 of these patients were in the group that received Awkly alone.

Table 3. Response to treatment (evaluable patients)

	Doxorubicin (n = 106)		Doxorubicin + HD-MPA (n = 104)	
Complete response	4	26%	6	38%*
Partial response	24		33	
No change	29		29	
Progressive disease	49		36	

*P = 0.08.

Table 4. Response to treatment by site

Site	Doxorubicin n	CR	PR	RR(%)	Doxorubicin + HD-MPA n	CR	PR	RR(%)
Skeletal	27	0	6	22	29	0	12	41*
Soft tissue	37	4	10	38	45	5	10	33
Lung	32	2	6	25	23	3	6	39
Pleural	9	0	2		16	0	8	
Liver	26	1	10	42	29	5	6	38
Visceral (lung+pleural+liver)	67	3	18	31	68	8	20	41

*P = 0.10. CR, complete response; PR, partial response; RR, response rate.

Response in the two groups according to localisation, i.e. skeletal, soft tissue or visceral (lung, pleural or liver), of metastases was also analysed (Table 4). There was a tendency for skeletal metastases to respond best (12/29 in the combined group versus 6/27 in the Awkly group, P = 0.10).

The median survival in both groups was 11 months [range 1–60 (+MPA) and 1–49 (−MPA) (Figure 1).

Awkly was generally well tolerated and only a few patients experienced vomiting and alopecia. Leucopenia or thrombocytopenia that necessitated postponement or cessation of treatment was not registered in any of the groups. Toxicity from HD-MPA was substantial, weight gain and fluid retention being the main problems experienced by more than half of the patients when the treatment time extended beyond 3 months. Vaginal bleeding after MPA withdrawal was seen regularly, but serious bleeding was not observed. Vaginal bleeding during treatment was seen in only a few cases.

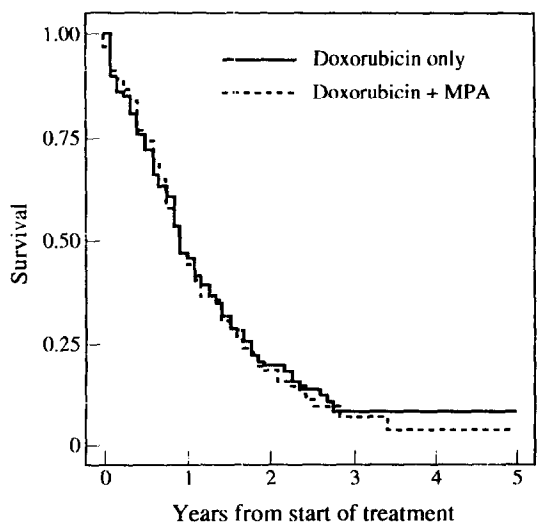

Figure 1. Life-table plot of survival from start of treatment for the two groups; doxorubicin alone (n = 111) and doxorubicin combined with HD-MPA (n = 107) in advanced breast cancer.

DISCUSSION

The two groups of patients were balanced with regard to age, disease-free interval and time from first metastases to randomisation. It is worth noting the relatively long time after first relapse before randomisation, which reflects the time for hormone treatment. Nevertheless, the response rate for Awkly was approximately 30% as we have reported for two other [8] clinical trials involving this regimen.

The response rate in the group of patients that received HD-MPA in addition to Awkly was non-significantly higher, although the response rate for skeletal metastases and the number of complete remissions (by site, see Table 4) tended to be somewhat higher in the combined group.

In patients with liver metastases, 5/29 in the combined group achieved a complete response (CR), with one still in complete remission (from multiple liver metastases) after 48 months, while 1/26 in the Awkly group had a CR of liver metastases.

Considerable side-effects from HD-MPA were seen, particularly weight gain and fluid retention. Detailed recording of body weight was not undertaken and more exact data can, therefore, not be given.

Since patients were selected on the basis of having disease proven to be resistant to hormone therapy according to rather strict criteria, it is unlikely that MPA induced responses via traditional mechanisms of action.

The present data support the results from our previous study with chemotherapy in combination with MPA [5], although the response rates and the differences in response rate between the study groups were smaller. This may be due to the selection criteria being different in the two protocols, but perhaps of more importance, is the fact that the time from first relapse until randomisation was 6–7 months in the previous study compared with 18–21 months in the present study.

It was observed in both studies that the effect of adding MPA to chemotherapy was most evident for patients with skeletal metastases, and there was a trend towards more complete responses (CRs). In the present protocol, 5/6 CRs of liver metastases were observed in the combination group.

When the two protocols ([5] and present manuscript) are viewed together, we think that we have provided clinical evidence for a possible interaction of chemotherapy and MPA, even in hormone-insensitive relapses and metastases, in concordance with experimental preclinical studies, resulting in an increased response rate. However, this has not been reflected in increased survival. Since unwanted side-effects are regularly observed for HD-MPA and considerable costs are involved, clearly this combination therapy must be regarded as experimental. However, an interaction between chemotherapy and HD-MPA in hormone-resistant breast cancer is new biological information of interest, and could be of clinical use, perhaps following further investigations of other gestagens (or other hormones) and differing doses.

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Adult Wilms' Tumour: Review of 22 Cases

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The Institut Gustave Roussy experience with nephroblastoma in 22 patients older than 16 years during a 19-year period (1973–1992) was retrospectively reviewed. All patients underwent a nephrectomy. There were 4 stage I, 8 stage II, 3 stage III and 7 stage IV patients. Initial postnephrectomy therapy included single modality approach in 7 patients (radiotherapy in 1 and chemotherapy in 6) and combined modality approach (radiotherapy and chemotherapy) in 15 patients. The agents used most often were actinomycin, vincristine and doxorubicin. 2 of 7 (29%) and 7/15 (47%) patients are disease-free survivors after first-line treatment. Salvage chemotherapy was given in 13 patients. Only 1 patient experienced a subsequent sustained complete remission. After a mean follow-up of 100 months (range 10–240), 12/22 patients (55%) are alive, including 10 who are disease-free (45%). We confirm that adult patients are likely to have more advanced disease and poorer prognosis than children. The combined modality approach is more active than one-modality therapy. Aggressive treatment, including the three-drug regimen actinomycin + vincristine + doxorubicin, regardless of stage, associated to irradiation starting from stage II, is recommended.

Key words: adult, nephroblastoma, Wilms' tumour, treatment
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INTRODUCTION

NEPHROBLASTOMA IS a disease of young children accounting for approximately 5–10% of all paediatric neoplasms. Although the occurrence of nephroblastoma in adults is infrequent, the exact incidence remains undetermined, since reports of adult patients before 1960 are difficult to interpret, and histopathological criteria for the diagnosis are not well defined [1, 2]. Thus, 80% of 192 cases gathered from the literature by Kilton and colleagues in 1980 were excluded because of lack of or unconvincing photomicrographs or incomplete histological descriptions [3]. However, Jagazia and colleagues found a 9.2% incidence of adults among patients with nephroblastoma seen at one institution during a 14-year period [4]. The incidence was estimated as 3% by Slevin and colleagues [5].

Compared to their paediatric counterparts, adult patients are assumed to have more advanced disease, relapse more frequently and respond poorly to therapy [6]. However, since 1979, a notable improvement in response and survival has been noted in adult patients when modern multimodal therapy is employed [7]. To better define the outlook of this disease in adults, we have reviewed our experience with patients older than 16 years of age with nephroblastoma treated in our institution between 1973 and 1992.

PATIENTS AND METHODS

Between 1973 and 1992, 22 patients ≥ 16 years old were referred to our institution for renal cell tumour defined histologically as nephroblastoma. Patients' characteristics, stage of disease, treatment and outcome were analysed according to a retrospective review of case files. All pathological specimens were reviewed at our institution and classified as either favour-

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