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Weekly Adriamycin® vs. 4-Epidoxorubicin Every Second Week in Advanced Breast Cancer. A Randomized Trial

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Abstract—*One hundred and sixty-six patients with advanced breast cancer previously not treated with chemotherapy for metastatic disease were randomly allocated to* 20 mg *Adriamycin® i.v. weekly (Awkly) as bolus injection or* 50 mg *4-epidoxorubicin biweekly over a* 3-h *infusion time (EPIbiwkly). Of the* 149 *patients evaluable for response, the response rate was* 36% *for Awkly vs.* 22% *for EPIbiwkly* (P = 0.10). *There was no difference in response duration or survival. The main difference between the two regimens was in toxicity. Seventy per cent of Awkly patients virtually had no side-effects vs.* 15% *in the EPIbiwkly group. Significant differences in favour of Awkly were observed both for nausea/vomiting and alopecia.*

INTRODUCTION

SEVERAL RANDOMIZED STUDIES have demonstrated that weekly infusions of low doses of Adriamycin® as single agent therapy is as effective as higher doses of chemotherapy delivered every 3–4 weeks, but is considerably less toxic [1, 2]. The main disadvantage of a weekly fractionation of Adriamycin® (Awkly) is frequent ward visits, although the treatment can almost always be given on an outpatient basis. Thus it was felt that attempts should be made to prolong the intervals between cycles while trying to maintain the good therapeutic index of the Awkly regimen. For this purpose 4-epidoxorubicin, which in clinical studies [3] has been shown to be less toxic than Adriamycin®, was given at a higher dose every second week. The dose was stipulated to be somewhat higher than the double dose of Adriamycin® since 4-epidoxorubicin has been claimed to be less myelosuppressive than Adriamycin® on a molar basis [4]. Pharmacokinetic studies [5, 6] have indicated that toxicity can be further reduced without loss of therapeutic activity when the infusion time is prolonged due to a reduction in maximum plasma concentration without a concomitant decrease in the area under the plasma concentration–time curve as compared to bolus injection. Accordingly, patients with advanced breast cancer were randomized to receive either Adriamycin® every week as a bolus injection or 4-epidoxorubicin by a 3-h infusion every second week.

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PATIENTS AND METHODS

From June 1984 to December 1986 a total of 166 patients with advanced breast cancer have been randomized.

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. Furthermore, patients previously treated with anthracyclines as adjuvant therapy or other cytostatics for metastatic disease did not enter the study.

All but one receptor negative patient had previously received hormone treatment and were considered as having metastatic disease resistant to hormone treatment.

Prior to initial treatment all patients underwent physical examination. Blood count, chest X-ray, bone isotope scan and/or bone survey radiographs and measurements of indicator lesions were obtained in all patients. If indicated by liver function tests, liver scan, sonography or computer tomogra-

phy was performed. Brain scans and/or computer tomography was performed in those patients who had symptoms or signs suggestive of central nervous system metastases.

Patients were allocated by random numbers to either Adriamycin® 20 mg every week (Awkly) or 4-epidoxorubicin 50 mg every second week for a 3-h infusion time (EPIbiwkly) (Table 1).

Blood counts were performed before each course of chemotherapy. When WCC and/or plt counts before start of treatment were between 3.0–3.9 and 100–124 × 10^9/l respectively, doses of chemotherapy were reduced by 25% and for the corresponding values of 2.0–2.9 and 75–99 × 10^9/l the dose reduction was 50%. For lower values treatment was postponed for 1 week.

The stipulated maximal cumulative dose was 750 mg/m^2 for both drugs. At least 2 months treatment was given before the first evaluation. Responding patients were treated until the stipulated maximal cumulative doses were reached and then received maintenance therapy with methotrexate 30 mg/m^2 and cyclophosphamide 600 mg/m^2 every 4 weeks for a total duration of chemotherapy of 2 years. Patients who did not respond (progressive disease) received a combination of 5-fluorouracil 1000 mg/m^2 days 1 and 2 and mitomycin-C 6 mg/m^2 day with courses repeated every 3 weeks (FuMi).

The main patient characteristics are summarized in Tables 2 and 3. There were no significant differences between the two groups with regard to important prognostic factors.

Table 1. Treatment regimes

Awkly	Adriamcyin® 20 mg q weekly (maximum cumulative dose 750 mg/m^2 as bolus injection)
EPIbiwkly	4-Epidoxorubicin 50 mg q 2 weeks by 3-h infusion (maximum cumulative dose 750 mg/m^2)

The criteria used for remission were those recommended by UICC [7].

Statistical methods

The comparability of the two treatment groups was assessed by performing the chi-squared test (with Yates' correction) for categorical variables and two-sample Student's *t*-test for means. For differences in response by site, Fisher's exact test was used. Survival curves were calculated by the actuarial life table method, and significance testing based on log-rank test [8].

RESULTS

A total of 166 patients were randomized. One hundred and forty-nine patients were considered evaluable for response and 160 for toxicity. Thirty-six patients had received adjuvant chemotherapy with CMF for 1 year (Table 4). None of the patients had received chemotherapy for metastatic disease previously. Eighty-one patients received Awkly and 79 EPIbiwkly. Eleven patients on EPIbiwkly refused further treatment after three courses or less due to excessive nausea and vomiting and were not considered evaluable for response. This leaves 81 Awkly patients who were fully evaluable, i.e. evaluable both for response and toxicity, while 68 patients treated with EPIbiwkly were evaluable for response and 79 for toxicity. The response rate for Awkly was 29/81 (36%, 95% confidence interval 25.7–47.3%) vs. 15/68 (22%, 95% confidence interval 13.3–34.1%) for EPIbiwkly ($P = 0.10$) (Table 5). Considering all patients that were randomized in each treatment arm, i.e. including patients where treatment was not given according to the protocol due to toxicity, the respective response rates were 29/81 (36%) for Awkly (all Awkly patients received treatment according to the protocol) and 15/79 (19%, 95% confidence interval 14.6–23.4%) for EPIbiwkly ($P = 0.03$). Responding sites were: soft tissue 11 Awkly patients (38%) and six EPIbiwkly patients (40%), skeletal metastases 14 (48%) and

Table 2. Main characteristics of patients evaluable for response

	Awkly	Percentage	EPIbiwkly	Percentage
No. of patients	81		68	
Mean age (years)	59		56	
Premenopausal	10	12	10	15
Postmenopausal	71	88	58	85
Disease-free interval (mean, months)	32		23	
Time from first metastases until randomization (mean, months)	15		15	
Hormone receptor status				
positive (≥10 pmol/g protein)	31	38	35	51
negative	8	10	4	6
unknown	42	52	29	43

Table 3. Localization of metastases

	Awkly		EPIbiwkly	
	n = 81	Percentage	*n* = 68	Percentage
Skeletal	20	25	22	32
Soft tissue	24	30	22	32
Visceral	37	33	24	35

nine (60%) respectively and visceral metastases 15 (51%) and eight (53%). Thus there were no significant differences with regard to response by site (*P* values 0.67–1.0 Fisher's exact test). The mean cumulative dose of Adriamycin® was 520 mg, i.e. 26 courses and a treatment duration of 26 weeks. The mean cumulative dose of 4-epidoxorubicin was 550 mg, i.e. 11 courses and a mean treatment duration of 22 weeks.

The median durations of complete remissions were 13.5 months for Awkly and 16 months for EPIbiwkly patients. For partial remissions, the median durations of response were 9.4 months and 10 months respectively (Table 6). There was no significant difference in survival between the two groups whether calculated from start of therapy (Fig. 1) or from time of diagnosis. The median survival in both groups was approximately 14 months. There was no difference with regard to response to second line chemotherapy which was approximately 20% in both groups. The Awkly regimen was well tolerated and only a few patients experienced vomiting or alopecia. In the EPIbiwkly arm a considerably larger proportion of patients (2–4 vs. 27–28%, $P < 0.00001$) complained of nausea and vomiting in conjunction to the treatment. Also more patients in the EPIbiwkly group developed alopecia (11 vs. 24%, $P = 0.05$) as compared to the Awkly group. No difference in WCC and plt counts before planned courses was registered (Table 7).

DISCUSSION

The two groups of patients balanced well according to age, disease-free interval and time from first metastases to randomization.

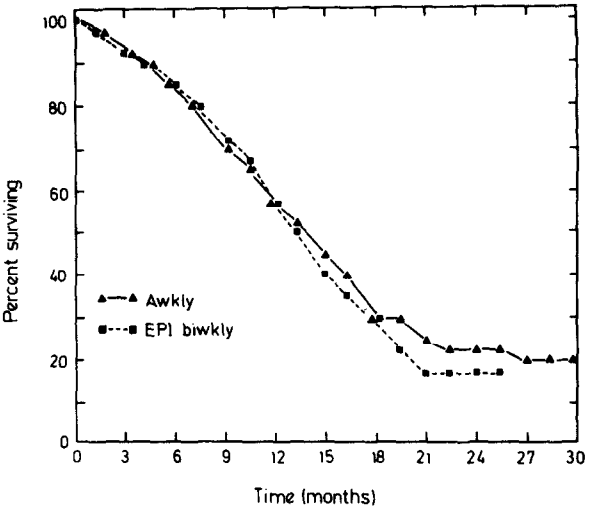

Fig. 1. Life table plot of survival from start of treatment for the two groups; Awkly (n = 81) *and EPIbiwkly* (n = 68) *in advanced breast cancer.*

Response rates for the two treatment arms did not differ significantly. The response rate to Awkly was similar to that observed in a previous study [2] (36 vs. 31%) with a similar selection of patients. In addition, the moderate toxicity of Awkly was reproduced in the current study. Extravasation was not experienced and has not been experienced in any of the 143 Awkly patients who have been included in the protocols. In some patients it was necessary to implant a vascular access port.

Recent pharmacologic studies [9] have demonstrated that Awkly can be assimilated at a continuous exposure to low drug levels with intermittent pulses. This original pharmacological profile could well be responsible for the antitumour effect that is now well documented. The toxicologic benefit might be explained by the peak attenuation phenomenon as demonstrated by Frenay *et al.* [9].

The main difference between the two regimens was toxicity. Seventy per cent of the Awkly patients had virtually no side-effects vs. 15% in the EPIbiwkly group. Significant differences in favour of the Awkly regimen were seen for both nausea/vomiting and alopecia. Thus, the experience with 50 mg of 4-epidoxorubicin delivered every second

Table 4. Previous therapy

	Awkly		EPIbiwkly	
	n = 81	Percentage	*n* = 68	Percentage
Surgery only	27	33	30	44
Surgery and local radiotherapy	26	32	12	18
Surgery and adjuvant chemotherapy	17	21	19	28
Local radiotherapy only	2	2	2	2
Hormone therapy				
tamoxifen	80	99	68	100
more than one hormone regimen	21	26	19	28

Table 5. Response

	Awkly $n = 81$	EPIbiwkly $n = 68$
CR	2	2
	36%*	22%
PR	27	13
NC	25	25
PD	27	26

*$P = 0.10$.

Table 6. Duration of response (months)

	Awkly		EPIbiwkly	
	Median	Range	Median	Range
CR	13.5	10–17	16.0	10–22
PR	9.4	2–27	10.0	2–23

week over a 3-h infusion time, with reduced maximum plasma concentration as compared to bolus injection, was disappointing with more toxicity than had been expected. This does not, however, imply that 4-epidoxorubicin is more toxic than Adriamycin®. On the contrary, there are now abundant data [10] that document less toxicity for 4-epidoxorubicin, especially reduced cardiotoxicity. What we have demonstrated in the present study is only that by doubling the dose of anthracycline and giving courses every second week instead of every week, even if delivered as a prolonged infusion, toxicity is increased considerably and the therapeutic index significantly reduced as compared to the weekly low-dose schedule. Manifest cardiotoxicity was not observed for any regimen. Bone marrow depression was negligible and did not cause postponement of planned courses in any group.

It can therefore be concluded that the efficacy and tolerability of weekly doses of doxorubicin (Awkly), as reported earlier, was confirmed in this study, and that higher doses of epirubicin given every second week (EPIbiwkly) were more toxic.

Table 7. Side-effects

	Awkly $n = 81$	Percentage	P values for differences	EPIwkly $n = 79$	Percentage
None	57	70	<0.0001	12	15
Nausea	2	2	0.0002	19	28
Vomiting	3	4	0.0001	21	27
Alopecia	9	11	0.052	19	24
Fatigue	8	10	0.07	17	22
Other (not specified)	2	2		2	2
Mean WCC × 10/l	4.9			5.5	
Mean plt × 10/l	281			293	

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