Prognostic role of amenorrhea induced by adjuvant chemotherapy in premenopausal patients with early breast cancer

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Summary The prognostic role of drug-induced amenorrhea (DIA) was restrospectively evaluated in 221 out of 254 consecutive premenopausal patients treated with adjuvant CMF or a CMF-containing regimen; 33 patients were eliminated because of lack of menstrual data. All patients had metastatic axillary nodes; drug regimens were: CMF × 9 courses; Tamoxifen (TM) and CMF × 6 courses; median age was 43 (range 26–54). Premenopausal status was defined as last normal menses within the 6 weeks preceding initiation of chemotherapy; DIA as cessation of menses for at least 3 months not later than 3 months from the end of chemotherapy. DIA occurred in 166/221 (75.1%) patients and was strictly related to the age of the patients; also, the older the patients the shorter the time required to develop DIA. At median follow up of 69 months, Mantel-Byar analysis showed a longer disease free survival (DFS) for patients who developed DIA as compared to others (DIA p proprn of women (P < 0.001). DIA prognostic value was independent of age, number of involved nodes, tumour size and number of CMF cycles, as assessed by the Cox model (RH 0.43, 95% CI. 0.24–0.77), in which DIA was entered as a time dependent covariate.

Adjuvant chemotherapy, especially cyclophosphamide, methotrexate and 5-fluorouracil (CMF), has been shown to significantly increase disease-free survival and overall survival of premenopausal patients with operable breast cancer (Bona donna et al., 1985; Early Breast Cancer Trialsist's Collaborative Group, 1988).

In similar groups of patients, surgical oophorectomy and ovarian radiation, as adjuvant to mastectomy, were also effective in reducing relapses and deaths (Nissen-Meyer, 1967; Bryant et al., 1981; Meakin et al., 1983).

Since cytotoxic chemotherapy is more effective in premenopausal than in postmenopausal patients (Early Breast Cancer Trialsist's Collaborative Group, 1988) and, in many cases, it induces ovarian failure with the occurrence of amenorrhea, a question arises about the relationship between the effect of adjuvant chemotherapy and the development of amenorrhea. In fact it has been suggested that drug-induced amenorrhea has beneficial therapeutic significance and that the effect of adjuvant chemotherapy is mediated, at least partly, through the suppression of endogenous hormone production.

While an association between drug-induced amenorrhea and longer disease free survival has been found by several authors in premenopausal patients with early breast cancer (Ludwig Breast Cancer Study Group, 1985; Padmanabhan et al., 1986; Brincker et al., 1987; Tormey et al., 1990), others have failed to do so (Bonadonna et al., 1985; Fisher et al., 1979), and thus the question remains still open (Editorial, 1989).

The aim of our study was to evaluate, restrospectively, if the development of drug-induced amenorrhea is associated with a prolongation of DFS in a series of consecutive cases of homogeneous premenopausal, node-positive patients with early breast cancer, treated with adjuvant CMF-containing regimens between 1978 and 1989.

Patients and methods

Selection criteria

The study included premenopausal women with histologically confirmed, non inflammatory unilateral stage II or III(T3a) operable breast cancer.

Premenopausal status was defined by the occurrence of the last normal menses within the 6 weeks preceding initiation of adjuvant chemotherapy.

Primary treatment was radical or modified radical mastectomy or quadrantectomy followed by radiotherapy of residual breast in small (T1) tumours. All patients had metastatic axillary nodes (N+).

Three adjuvant CMF containing regimens were employed: (a) CMF for nine courses plus Tamoxifen (TM), 30 mg day–1 for 2 years; (b) CMF alone for nine courses; (c) CMF alone for six courses. The CMF regimen was cyclophosphamide 100 mg m–2 orally on days 1–14, methotrexate 40 mg m–2 and 5-fluorouracil 600 mg m–2 intravenously on days 1 and 8 of each 28 day cycle. Patients were eligible for adjuvant chemotherapy if white blood cell count was 4 × 109–1 or more, platelet count 100 × 109–1 or more and serum creatinine, bilirubin and aminotransferase were within normal levels.

Sixty-eight percent of patients were enrolled in two controlled clinical trials; one of which has been previously reported (Bianco et al., 1988).

Definition of amenorrhea

Patients were considered to have drug-induced amenorrhea (DIA) if cessation of menses occurred no later than 3 months from the completion of chemotherapy, and lasted for at least 3 months; the first day of the last menstrual cycle was taken as the time of onset of amenorrhea. Amenorrheic patients who resumed some menstrual function during follow up have been defined as temporary DIA.

Patients who maintained normal menses beyond 3 months after the end of chemotherapy, were considered non amenorrheic (NA).

Details of patients

From February 1, 1978 to March 1, 1989, 259 consecutive patients were included into the study.

Thirty-eight patients were not evaluable for the analysis: in 28 the menstrual history was incomplete, two patients had uncertain records of the beginning and ending of therapy and eight patients refused the assigned adjuvant treatment. Thus, 221 patients were analysed. The main characteristics of the patients are summarised in Table 1. Median age was 43 (range 26–54). CMF-9 cycles ± TM (56 and 57 patients, respectively) were the two arms of a randomised controlled...
trial (Bianco et al., 1988), and no difference was found in DFS between the two treatment groups. Thus, in the present study, they have been considered equivalent and two classes of length of therapy have been defined: nine and six CMF cycles.

Statistical methods

Starting date for the follow up was initiation of CMF therapy. Termination date for the analysis was March 1st, 1990, when the median follow up was 69 months.

DFS was defined as the time from beginning of therapy to when either recurrent disease was ascertained or was suspected and later confirmed. Failure was defined as any first recurrence including contralateral disease; no death was observed without recurrence. Time to amenorrhea was the interval between the date of the last menstrual cycle and the beginning of CMF therapy; when negative values were observed, as a consequence of the definition of DIA, a shift to the first day following initiation of therapy was done.

Kaplan-Meier method (1958) was used to estimate DFS curves for baseline prognostic factors; statistical significance of DFS difference was assessed by Mantel-Haenszel test (Mantel, 1966). In studying amenorrhea, life-time analyses were performed taking into account the transient nature of the menstrual status: cessations of menses, indeed, as consequence of the therapy, do arise at a sometime after the starting of the treatment. Thus, a potential temporal bias exists in classifying a subject as amenorrheic or not, since the length of disease-free follow up could affect the chance of amenorrhea to be induced (Anderson et al., 1983). Even though the magnitude of the bias is likely to be small, because most of DIA occur shortly after the therapy, an appropriate analysis was performed using a method first published by Mantel and Byar (1974), in which subjects (amenorrhea yes/no) are compared according to their response status at each time of the follow up. Graphical representation of DFS curves was made according to Simon and Makuch (1984): non relapsed subjects at a given arbitrary time-origin t_o, from the beginning of follow up, are classified in two groups according to whether they have or have not experienced DIA before t_o. For the non amenorrheic group, DFS curve estimates the probability of not relapsing beyond any time t_o greater than t_o, conditional upon being in NA status at t_o. Subjects who eventually became amenorrheic are censored at the time they cross to the DIA group. For amenorrheic ('responders') patients, DFS curve estimates the probability of not relapsing beyond t_o, t_o > t_o, given either they are in DIA status at t_o or enter it in the interval between t_o and t_o. As suggested by Simon and Makuch, in our study, t_o was fixed at 12 weeks after the onset of therapy, when more than half of patients had experienced DIA. For example, a patient who develops amenorrhea at 8 weeks is always considered to have been amenorrheic, from the 12th week (t_o) until relapse or last follow up. Conversely a patient who becomes amenorrheic at 36 weeks remains in the non-amenorrheic group from 12 weeks (t_o) to 36 weeks, when she is censored. This same patient is then considered in the amenorrheic group from the time of development of amenorrhea until relapse or last follow up. In the 'landmark' method (Anderson et al., 1983), instead, groups are defined according to the menstrual status at a given 'landmark' time t_o, regardless of any subsequent variation during the follow up. In our study no relapse was observed before t_o, time; therefore no patient was excluded from the computations. Multivariate adjustment for other baseline prognostic factors was performed by a Cox's regression model (Cox, 1972), where amenorrhea (yes/no) was entered as a time-dependent covariate (BMDP, 1988).

Results

Amenorrhea occurred in 166/221 (75.1%) patients. Twenty amenorrheic patients (12%) resumed some menstrual activity between 4 and 29 months after cessation of menses (temporary DIA). Time to onset of DIA ranged between 21 and 342 days from the beginning of cytotoxic chemotherapy (median 53 days). Negative values refer to eight patients, aged 43–53, who had their last menstrual cycle 21 to 5 days before the starting of therapy. No significant correlation was found between DIA and number of involved axillary nodes or tumour size, while occurrence of amenorrhea was significantly associated with number of CMF cycles (Table II). A significant correlation was also found between the development of amenorrhea and the patient's age: the younger the patients the lower the incidence of DIA. Among amenorrheic patients a decreasing percentage of temporary DIA was observed with increasing age. Furthermore, an inverse linear correlation (Figure 1) was observed between the patient's age and the time required to produce amenorrhea (r = -0.42; P < 0.001).

One hundred and two relapses were observed during the follow up. DFS of amenorrheic patients was significantly better than that of patients who maintained normal menses (Mantel-Byar chi-square = 10.95, P < 0.001; relative hazard = 0.50). DFS curves for DIA and NA patients, as shown in Figure 2, take into account the time-dependent nature of menstrual status according to Simon and Makuch. Time-origin is arbitrarily fixed at 12 weeks after the beginning of treatment. At that time, 121 out of the 166 DIA subjects (72.9%) had already become amenorrheic.

Table I Characteristics of patients

| Variable          | No. | %  |
|-------------------|-----|----|
| Total number      | 221 |    |
| Age               |     |    |
| ≤ 35              | 28  | 12.7|
| 36–40             | 39  | 17.6|
| 41–45             | 75  | 33.9|
| 46–50             | 61  | 27.6|
| > 50              | 18  | 8.1 |
| Positive nodes    |     |    |
| 1–3               | 105 | 47.5|
| > 3               | 116 | 52.5|
| Tumour size       |     |    |
| ≤ 2 cm            | 46  | 20.8|
| 2.1–5 cm          | 121 | 54.8|
| > 5 cm            | 27  | 12.2|
| unknown           | 27  | 12.2|
| Adjuvant therapy  |     |    |
| CMF-9 cycles ± TM | 113 | 51.1|
| CMF-6 cycles      | 108 | 48.9|

Table II Association between drug-induced amenorrhea and other patient variables

| Variable | NA | DIA | Permanent | P     |
|----------|----|-----|-----------|-------|
|          | No. of cases (%) |       |           |       |
| Age      |     |     |           |       |
| ≤ 35     | 25  | 89.3| 3 (10.7)  | –     |
| 36–40    | 21  | 53.8| 5 (12.8)  | 13 (33.3)|
| 41–45    | 6   | 8.0 | 9 (12.0)  | 60 (80.0)|
| 46–50    | 1   | 1.6 | 3 (4.9)   | 57 (93.4)|
| > 50     | 2   | 11.1| –         | 16 (88.9)|
| No. of positive nodes |     |     |           |       |
| 1–3      | 25  | 23.8| 6 (5.7)   | 74 (70.5)|
| > 3      | 30  | 25.9| 14 (12.1) | 72 (62.1)|
| Tumour size |     |     |           |       |
| ≤ 2 cm   | 9   | 19.6| 3 (6.5)   | 34 (73.9)|
| 2.1–5 cm | 36  | 29.8| 13 (10.7) | 72 (59.5)|
| > 5 cm   | 6   | 22.2| 3 (11.1)  | 18 (66.7)|
| unknown  | 4   | 14.8| 1 (3.7)   | 22 (81.5)|
| No. of CMF cycles |     |     |           |       |
| 9 cycles | 17  | 15.0| 13 (11.5) | 83 (73.5)|
| 6 cycles | 38  | 35.2| 7 (6.5)   | 63 (58.3)|
Prognosis was also found to be associated with number of positive nodes and tumour size, while no relationship was apparent between DFS and age either considering 5 year cut offs (Table III) or a single cut off at 40 years (age ≤ 40: O/E = 1.28; age > 40: O/E = 0.98; P = 0.08). Duration of therapy (nine vs six CMF cycles) did not influence DFS.

Multivariate evaluation of the prognostic role of DIA was performed by a Cox regression analysis, where menstrual status was entered as a time-dependent covariate. Other covariates were age, number of positive nodes, tumour size and number of CMF cycles (Table IV). DIA was confirmed to be independently associated with a better prognosis (RH = 0.43; 95% CI 0.24–0.77). Number of positive nodes and tumour size were also found to significantly affect DFS. No interaction was evident between menstrual status and other conventional prognostic factors.

A similar analysis was performed to evaluate a possible effect of DFS of resuming some menstrual activity during follow up. Time-dependent analyses on the 166 amenorrheic cases showed no difference in DFS between temporary and permanent DIA patients (Mantel-Byar chi-square = 0.77, 0.30 < P < 0.40).

Discussion

The efficacy of adjuvant chemotherapy in reducing recurrences and deaths in premenopausal node positive breast cancer patients has been confirmed in a number of studies. However, it is still controversial if the benefit of cytotoxic chemotherapy could be mediated, at least partly, by the drug induced suppression of ovarian function.

Analysis and comparison of the data is difficult because of a number of open questions in different studies.

First of all premenopausal status has been varyingly defined. Some studies (Bonadonna et al., 1985; Padmanabhan et al., 1986; Tormey et al., 1990) used a rather wide criterion to define premenopause which included women without menstral activity up to 12 months. The Ludwig Breast Cancer Study Group (1985) evaluated the role of DIA in patients who had their last menses within 6 months prior to initiation of chemotherapy; however, a similar DFS was observed in the subgroup of patients who had their last menses within 6 weeks prior to beginning of adjuvant chemotherapy. In order to ensure that amenorrhea was drug-induced rather than physiologic we adopted a restrictive criterion to define premenopausal status such as the occurrence of the last normal menses within the 6 weeks preceding the beginning of therapy.

Another important aspect is the definition of DIA. We believe that, in order to consider amenorrhea as drug-related, this definition should be inclusive of both a minimum duration of the amenorrhea itself and a defined period of its onset from the end of the therapy. While data are lacking on the latter question, there is a general concordance (Fisher et al., 1979; Bonadonna et al., 1985; Ludwig Breast Cancer Study Group, 1985; Padmanabhan et al., 1986; Brincker et al., 1987) in defining DIA as cessation of menses for at least 3 months, except for the Eastern Cooperative Oncology Group (ECOG) study (Tormey et al., 1990) in which drug-related amenorrhea is defined as 12 months without menstral activity.

In our study, as well as in others (Fisher et al., 1979; Bonadonna et al., 1985; Ludwig Breast Cancer Study Group, 1985; Padmanabhan et al., 1986; Tormey et al., 1990), a close relationship between induction of amenorrhea and age of the patient is evident, the older the patient the greater the incidence of DIA. Furthermore, we observed an inverse correlation between the time to onset of DIA and patient’s age. These results seem to be the signal of the increasing ovarian
sensitivity to cyclophosphamide in older women approaching to physiological menopause, as suggested by Rose and Davis (1980).

The variable definition of premenopausal status and DIA, age distribution of patients and therapeutic regimens might account for the wide range (32–87%) of DIA occurrence reported in the literature (Fisher et al., 1979; Bonadonna et al., 1985; Ludwig Breast Cancer Study Group, 1985; Padmanabhan et al., 1986; Brincker et al., 1987; Torney et al., 1990). In our study DIA occurred in 75% (166/221) of patients, in 31% of women 40 years or younger and in 94% of those older than 40. Twenty patients (12%) resumed normal menses after temporary DIA. Although temporary DIA could be the expression of a partial suppression of ovarian function, and thus associated with a different prognosis, we did not find a significant difference in DFS among amenorrheic patients with temporary and permanent DIA. However, this result might be affected by the low number of patients who resumed menses. Only the Ludwig Breast Cancer Study Group (1985) dealt with this question, with similar results.

Finally, the time dependent nature of amenorrhea might somehow affect the correlation between DIA and DFS (Anderson et al., 1983). This potential bias, however, is probably small because of the general early occurrence of cessation of menses following initiation of therapy. To overcome this bias, in our study, we employed the Mantel-Byar procedure (Mantel & Byar, 1974) in univariate analysis and the Cox proportional hazard regression model (Cox, 1972) in which amenorrhea is a time varying covariate, as it was done in the ECOG study (Tormey et al., 1990).

The relationship between DIA and length of DFS was analysed in several studies with conflicting results. In the Milan trial (Bonadonna et al., 1985) only patients younger than 41 were analysed for DFS as related to DIA, since only two patients older than 40 maintained normal menses. Thus, analysis was carried out on a small number of cases, i.e. 19 nonamenorrheic and 13 amenorrheic patients, and the conclusion was that DFS was not affected by DIA. The 10 year DFS was 31.6% and 37.2% for the two groups, respectively. In addition, the same authors reported that salvage castration at first relapse induced a higher response rate in patients who had experienced DIA as compared to those who had not (30 vs 20% response rate). Based upon these findings they concluded that DIA is not equivalent to complete ovarian failure; this opinion, based on a low number of events, is contrasting with the data of others who assessed ovarian function by measuring levels of circulating sexual hormones during adjuvant chemotherapy (Koyama et al., 1977; Fisher et al., 1979; Rose & Davis, 1980; Ludwig Breast Cancer Study Group, 1985; Padmanabhan et al., 1987), including ourselves (Delrio et al., 1986).

The National Surgical Adjuvant Breast Project group (Fisher et al., 1979) reported a lack of association of DIA with depressed ovarian function induced by melphalan. Since improvement of DFS was slightly better in younger patients, who had lower incidence of DIA, as compared to older women, it could be concluded that ovarian suppression was not a role. However, no analysis was carried out to evaluate the real relationship between occurrence of DIA and effect of therapy.

By contrast, the Ludwig Group’s Trial I (1985) showed that amenorrhea induced by CMF-containing regimens was significantly associated with a longer disease-free survival, in younger patients, in patients who received lower CMF doses and in patients with ER+ tumours; it was, thus, suggested that chemotherapy might influence tumour growth by suppression of ovarian endocrine function, besides exerting a direct cytotoxic effect.

Similarly, in the ECOG trial (Tormey et al., 1990) patients developing DIA during adjuvant therapy with CMF, CMFP or CMFPT had a highly significant better survival.

The Danish Breast Cancer Cooperative Group (Brincker et al., 1987) found, in a prospective randomised trial, that cyclophosphamide alone was effective in improving DFS only in patients who experienced DIA, differently from CMF which was active in DIA as well as in NA patients. It was suggested that the effect of chemotherapy could be mediated partly through ovarian suppression and partly through a purely cytotoxic mechanism, the latter being more evident when combination chemotherapy (CMF) was used.

Finally, in 1986, the Manchester group (Padmanabhan et al., 1986) reported, in a randomised trial comparing CMF, with observation, that a significant improvement of 3-year DFS and OS was seen only in premenopausal patients who experienced CMF induced permanent amenorrhea: DFS of CMF-treated non amenorrheic patients was similar to that of untreated controls. However, recently the same group reported in abstract form (Richards et al., 1990) that, at the 8-year update of the study, the importance of DIA, in patients younger than 41, has lessened. Since a full-length paper is not available, it is difficult to discuss this result.

Our data show the existence of a significant correlation between DIA and prolongation of DFS. The prognostic relevance of DIA is independent of number of positive nodes, tumour size and number of CMF cycles. These results are consistent with those reported by the majority of studies that could adequately document amenorrhea.

Although the existence of a strong statistical association does not necessarily mean that DIA is causally related to a better prognosis in early breast cancer, and amenorrhea might only be a marker of a greater chemotherapy-induced tumour cell kill (International Breast Cancer Study Group, 1990), our results strongly suggest that the suppression of ovarian function could play a relevant role in the mechanism of action of adjuvant cytotoxic therapy in premenopausal breast cancer patients.

The beneficial effect of oophorectomy in both advanced and early disease, the recent results with LHRH analogues, which produce complete suppression of ovarian function, in patients with advanced disease, the relationship between DIA and improved DFS could suggest that adjuvant hormone-therapy, e.g. LHRH superagonist ± Tamoxifen, might have some effect in premenopausal patients. However, there is no evidence that the effect of endocrine therapies will be as large as chemotherapy. In fact, a recent paper of the International Breast Cancer Study Group (Goldhirsch et al., 1990) shows that chemotherapy provides additional cytotoxic effect over and above those attributable to endocrine mechanisms alone. Whether endocrine therapies can replace chemotherapy for subset of premenopausal women with presumably hormone-responsive primaries is a matter for future clinical trials.

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