Original article

Annals of Oncology 15: 79–87, 2004
DOI: 10.1093/annonc/mdh016

Epirubicin–cyclophosphamide adjuvant chemotherapy plus tamoxifen administered concurrently versus sequentially: randomized phase III trial in postmenopausal node-positive breast cancer patients. A GEICAM 9401 study

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On behalf of the GEICAM Group

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Received 10 April 2003; revised 12 August 2003; accepted 28 August 2003

Background: A prospective randomized clinical trial was implemented to assess whether the concomitant or the sequential addition of tamoxifen to chemotherapy provides improved clinical benefit in the adjuvant treatment of breast cancer in postmenopausal patients.

Patients and methods: Four-hundred and eighty-five patients with node-positive operable disease were randomized to receive tamoxifen (20 mg/day) concomitantly (CON) or sequentially (SEQ) to EC chemotherapy (epirubicin 75 mg/m^2 + cyclophosphamide 600 mg/m^2 on day 1, every 21 days for four cycles).

Results: In the 474 fully evaluable patients there were 96 events; eight being second neoplasms and 88 being related to the breast cancer. Of these, 48 of 88 occurred in the CON arm and 40 of 88 in the SEQ arm. The Kaplan–Meier estimation of disease-free survival (DFS) at 5 years was 70% in the CON and 75% in the SEQ group (log-rank test, $P = 0.43$). Adjusted hazard ratio for treatment was 1.11 (95% confidence interval 0.71–1.73; $P = 0.64$).

Conclusion: This study fails to show an advantage of one treatment arm over the other, but a trend, albeit non-significant, appears to favor the sequential addition of tamoxifen to epirubicin + cyclophosphamide and, as such, warrants further investigation.

Key words: adjuvant chemotherapy, adjuvant tamoxifen, breast cancer, concomitant, cyclophosphamide, epirubicin, sequential

Introduction

Some clinical investigators hypothesized, in the early 1980s, a possible antagonistic interaction between tamoxifen (TAM) and chemotherapy [1]. The biological mechanism for such an effect would be cytokinetic in that the effectiveness of the chemotherapy might be diminished by alterations in tumor cell kinetics induced by TAM. Clinical data consistent with this statement came from NSABP B-9 [2]. Tamoxifen added to melphalan–5-fluorouracil (PF) chemotherapy was associated with a lower probability of disease-free survival (DFS) in patients aged <50 years and who were estrogen receptor negative. Five-year results of this trial showed a poorer overall survival for this patient subgroup [3]. However, the use of TAM added to PF was clearly beneficial for postmenopausal, estrogen receptor positive women.

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Basic research on the interaction between TAM and chemotherapy has been conducted in different laboratories and the findings yielded some insight with respect to the complexity of this issue. Interactions that were different from straightforward cytokinetic effects were reported and included several biochemical, pharmacological and biological interactions with different chemotherapy agents. Conflicting observations with respect to the most commonly used chemotherapy drugs undermined the credibility of the clinical relevance of the findings. For example, melphalan showed uniform antagonism [4, 5] and, while a synergism between 5-fluorouracil and TAM was reported by one group [4], the contrary was observed in other laboratories [5–7]. Similar contradictory results were published with doxorubicin, which was shown to be additive [5] or antagonic [7, 8] in different laboratories. Given the heterogeneity in the spectrum of interactions between TAM and chemotherapeutic agents, the net effect on the patient could be quite unpredictable.

The existing clinical experience with metastatic breast cancer has been of limited help on this issue. Although response rates improved slightly there were no demonstrable survival benefits in favor of combined chemo-endocrine therapy in a randomized clinical trial [9]. Interpreting these findings was challenging because they were consistent with not only a lack of interaction between TAM and chemotherapy but also with a less than additive interaction [10]. The existing contemporary experience regarding the adjuvant setting was summarized in the 1992 version of the meta-analysis conducted by the EBCTCG [11]. The conclusions with regard to postmenopausal women were that the risk of disease recurrence was lower when combining TAM with the chemotherapy than with any of the therapies used alone. These conclusions were translated into recommendations for clinical practice by the panel of Sant Gallen International Conference [12] but "the proper sequencing of chemotherapy and tamoxifen remains to be defined". This 1992 meta-analysis was based, largely, on the NSABP B-16 results, a trial which used TAM and chemotherapy simultaneously and from which the authors interpreted their positive results as a demonstration of an absence of unfavorable interaction between TAM and the different chemotherapy regimens used in the trial. As a logical conclusion the authors stated: "…until studies prove that delaying the administration of TAM until completion of chemotherapy results in a greater benefit, administering the two modalities simultaneously is an appropriate treatment strategy".

In order to clarify the doubts regarding the sequence of chemotherapy and TAM administration in the adjuvant therapy of breast cancer, we decided to implement a prospective randomized clinical trial.

Patients and methods

Eligibility

Postmenopausal women with primary operable breast cancer and at least one histologically verified positive axillar node involvement were eligible. Postmenopausal status was defined as the last menstruation having occurred at least 1 year before treatment, a previous ovariectomy, or follicle-stimulating hormone (FSH)/luteinizing hormone (LH) levels >40 mU/ml. Upper age limit was settled at 70 years. Prior to randomization, chest X-ray, blood biochemistry and bone scan were performed. In case of elevation of liver enzymes, a computed tomography (CT) scan or sonography of the liver was mandatory. Upper limit of time-lapse allowed between surgery and the first chemotherapy administration was 6 weeks. Exclusion criteria were metastatic disease, locally advanced breast cancer, cardiac disease, and any other ailment adjudged by the clinical investigator as inappropriate for inclusion. Hormone receptor status, whether positive or negative, was not an exclusion criterion. The ethical committees of the participating institutions approved the study. All patients provided written informed consent and the ethical considerations conformed to the Helsinki Declaration as well as to Spanish legislation and regulations.

Randomization, stratification and treatment

The trial was designed to answer a single question, i.e. whether administration of TAM concurrently (CON) or sequentially (SEQ) to scheduled chemotherapy could offer clinical benefit to the breast cancer patient. The only difference between the two treatment arms was the starting point of TAM administration. A central randomization procedure was performed with stratification by center and surgical procedure (lumpectomy or mastectomy). Allocation to CON or SEQ was carried out in blocks of eight patients, established according to a table of random numbers. Patient number and treatment group assignment was communicated to the investigator on request by telephone call and confirmed by fax. Patients were to receive epirubicin (75 mg/m^2) plus cyclophosphamide (600 mg/m^2) intravenously every 21 days, for four cycles. We deliberately chose an equivalent regimen to that of the NSABP AC trial but with fewer risks of cardiotoxicity. We estimated the epirubicin dose of 75 mg/m^2 as being equivalent to 60 mg/m^2 of doxorubicin, based on published data [13, 14]. All patients were to receive TAM 20 mg daily by mouth for 5 years. Patients randomized to the CON arm were to take their first dose on day 1 of the first cycle of chemotherapy while the patients randomized to the SEQ arm commenced TAM on day 21 after the fourth cycle.

Study objectives and statistical considerations

Statistical estimation of the number of patients needed presented some challenges. There were no clinical antecedents to provide an indication regarding the size of the difference nor the direction of benefit to be expected. Pre-clinical data were contradictory with respect to doxorubicin and TAM interactions, so neither synergism nor antagonism could be factored into the calculations. As already stated, the 'success' of concurrent administration of anthracycline + TAM was somewhat ambiguous since the combination was considered better than TAM alone, but the results did not exclude the possibility of an even better outcome in the case of there being an antagonistic effect between anthracycline and TAM. Hence we chose a bilateral test so as not to pre-judge the direction of treatment advantage. Due to the unavoidably arbitrary nature of the choice and taking into account feasibility considerations, we opted for a 10% difference in 5-year disease-free survival (DFS) between treatment arms while acknowledging that even 1% difference would be clinically relevant. The primary goal was 5-year DFS and, for the purposes of the statistical analyses, an event was defined as the first documented evidence of local, regional or distant recurrence, recurrence of tumor in the ipsi-lateral breast following lumpectomy, second primary cancer, or death without recurrence of cancer. In consideration of the meta-analysis data, we set the expected 5-year DFS at 50%. The statistical significance of the difference between DFS distributions by treatment was determined by log-rank test [15]. For an α risk of 5%, a power of 80%, a proportion of events in the control arm of 0.5, and a difference in the proportion of events between the two arms of 0.1, and a two-sided test of probability, the number of patients needed was estimated as 362 per treatment arm [16].

A multiple proportional Cox model was performed to test the value of the treatment while adjusting for the main prognostic factors.

The proposed recruitment period was 3 years, and an interim analysis was planned for 2 years later. The trial was opened to recruitment in June 1995.

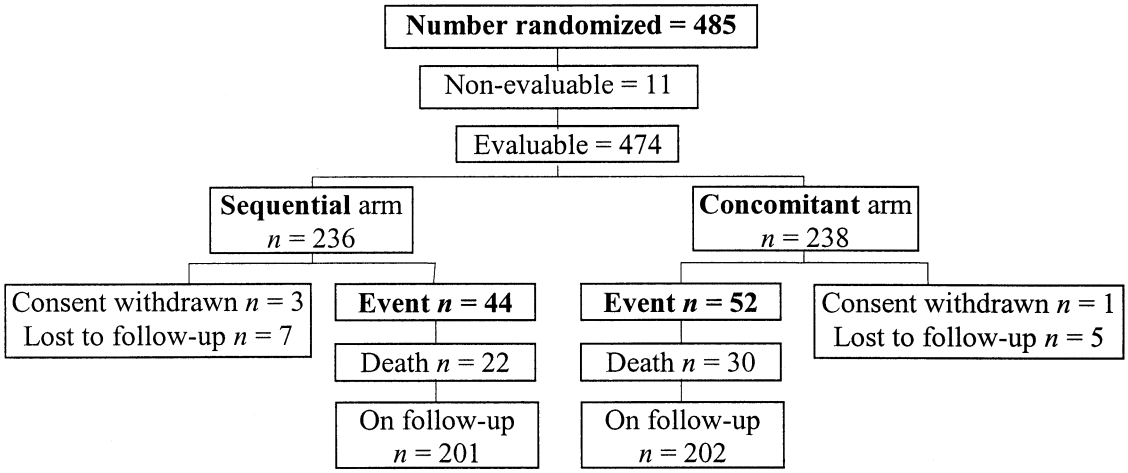

Figure 1. Trial status at present: main facts, figures and events.

Recruitment was running slower than planned and by the third year the required number of patients was not reached. The Steering Committee of GEICAM decided to prolong the recruitment period for two more years. By July 2000 the problem of recruitment persisted and the Steering Committee opted to close the enrolment.

Results

A total of 485 patients were recruited and randomized in 29 GEICAM-affiliated centers. A flowchart of main features of the study design and execution is shown in Figure 1. Of the 485 patients, 11 (2.26%) were non-evaluable because of major protocol deviations; six patients were ineligible because of metastatic disease, two patients were in stage IIIB, two patients were premenopausal and one patient did not have documented nodal involvement. Analysis of results was performed according to the intent-to-treat principle and, as such, patients with minor protocol deviations or treatment noncompliance were not excluded. At a median follow-up of 54 months, seven patients were lost to follow-up in the SEQ treatment arm and five patients in the CON arm. Additionally, three and one patient, in the two treatment arms, respectively, opted to withdraw from the study. Minimum time of follow-up was 22 months and the maximum time was 83 months. Patient characteristics are depicted in Table 1. As expected after stratification and randomization, the main demographic characteristics and prognostic factors were well balanced in the two treatment groups. Hormone receptor determination was by immunohistochemistry in all participating centers. Local criteria for positive or negative status were respected when results were expressed unambiguously. A threshold of ≥10% positive cells was preferred when this quantitative information was available. Compliance with treatment was generally good, with 87% and 90% chemotherapy cycles administered on time for SEQ and CON treatment arms, 11% and 9%, respectively, were delayed <5 days, with only 2% and 1%, respectively, being delayed >5 days. As per protocol, delayed chemotherapy administration was justified on the grounds of granulocyte count <1000/ml or any clinically serious condition, as judged by the patient or investigator. Dose reduction was justified on the grounds of induction of neutropenic fever. Overall, dose reduction was necessary in 10% of patients in the SEQ group and in 12% of patients in the CON treatment arm.

Outcomes

At the time of database closure, 96 events and 52 deaths were registered. The incidence of recurrence and second neoplasm with respect to treatment group is listed in Table 2. A higher rate of occurrence of every type of event was observed consistently in the CON treatment arm, albeit the numbers are relatively small. The total breast cancer related events were 88, of which 48 of 88 occurred in the CON arm and 40 of 88 in the SEQ arm. Most of them, 80 of 88 (91%), were distant metastasis, and their distribution with respect to treatment arm followed the same proportion: 43 of 80 in the CON arm versus 37 of 80 in the SEQ arm. Second neoplasm incidence is also shown in Table 2. No differences between treatment arms in the total numbers of second neoplasms were observed.

The Kaplan–Meier estimates for 5-year DFS were 70% for patients treated in the CON group compared with 75% in the SEQ treatment arm (overall log-rank test 0.43; Figure 2). The DFS plots of both treatment arms are almost identical until the third year of follow-up, at which stage they diverged and followed a trend in favor of the SEQ treatment arm. Statistically significant prognostic factors on univariate analysis were the number of axillar nodes involved, histology grade, and hormone receptor status (data not shown). Multivariate regression analysis confirmed the same prognostic factors. Cox proportional hazard model that included these three significant prognostic factors plus the treatment arm variable is presented in Table 3. The adjusted hazard ratio with respect to treatment arm was 1.11 with a 95% confidence interval (CI) between 0.71 and 1.73 ($P = 0.64$).

Table 1. Characteristics of the patients segregated with respect to treatment arm assignment

Characteristic	Sequential		Concomitant	
	No. of patients	%	No. of patients	%
Patient assignment	236	49.8	238	50.2
Age, years				
Median (mean)	63 (62.0)		62 (61.4)	
Range	47–75		48–75	
Weight, kg				
Median (mean)	69 (69.4)		69 (70.5)	
Range	37–102		44–114	
Surgery				
Lumpectomy	73	30.9	65	27.3
Mastectomy	163	69.1	173	72.7
Tumor size				
T1	72	30.6	64	27.5
>T2	163	69.4	169	72.5
Metastatic nodes				
1–3	149	63.1	164	69.2
4–9	65	27.5	58	24.5
>10	22	9.3	15	6.3
Hormone receptor status				
Estrogen-negative (ER–)	41	17.4	39	16.4
Estrogen-positive (ER+)	167	70.8	164	68.9
Status unknown	28	11.9	35	14.7
Progesterone-negative (PgR–)	70	29.7	72	30.3
Progesterone-positive (PgR+)	121	51.3	122	51.3
Status unknown	45	19.1	44	18.5
Combined ER– and PgR–	36	15.3	32	13.4
Combined ER+ and/or PgR+	174	72.7	172	72.3
Unknown	26	11.0	34	14.3
Histology grade				
1	33	14.0	34	14.3
2	112	47.5	97	40.8
3	65	27.5	78	32.8
Unknown	26	11.0	29	12.2

Subgroup analysis was performed to assess the possible influence of hormone receptor negative patients included in the study. Although the subgroup numbers were very small, no trend was observed in regard to differences in the number of events in this subgroup of hormone receptor negative plus hormone receptor status unknown patients (Figure 3).

Toxicity

Acute toxicity data are presented in Table 4. Neutropenic fever was reported in 15 of 927 (1.61%) cycles of the SEQ treatment arm and in nine of 941 (0.95%) cycles of the CON arm. No significant differences between treatment groups were observed in the incidence of any of the toxicities. A special vigilance was implemented with respect to thromboembolic phenomena due to previous reports that had raised concerns regarding an increased incidence of these types of events when combining chemotherapy with TAM [17, 18]. Table 5 contains the thrombotic events reported during the chemotherapy administration phase. Forearm phlebitis incidence was seven for the SEQ and six for the CON treatment group. One patient in each group suffered cerebrovascular accident (CVA). There were four episodes of deep vein thrombosis (DVT) of the legs in the CON group compared to one episode in the SEQ treatment group. The only episode of pulmonary embolism (PE) was registered in the SEQ treatment arm. Our understanding is that this period of time is the only one

Table 2. Pattern of events segregated by treatment arm

Event	Sequential		Concomitant		Total	
	No. of patients	%	No. of patients	%	No. of patients	%
Metastases	37	42	43	49	80	91
Nodal regional recurrence	1		2		3	
Local recurrence	2		3		5	
Total breast cancer related events	40	45	48	55	88	100
Second neoplasm	4		4		8	
Endometrial carcinoma	2					
Colorectal cancer	1		2			
Gastric cancer			1			
Contralateral breast			1			
Soft tissue carcinoma	1					
Overall total number of events	44		52		96	

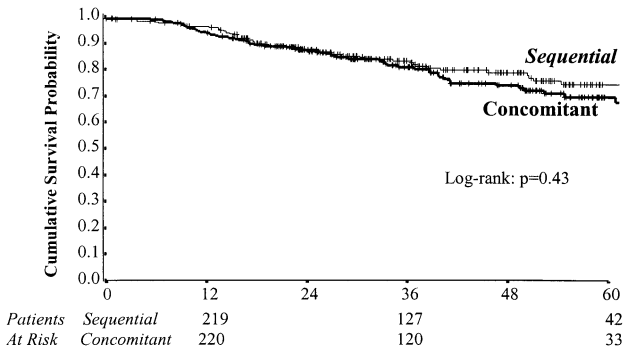

Figure 2. Kaplan–Meier plot of disease-free survival time for concomitant and sequential treatment arms. Censored patients are represented as dots on the lines and the number of remaining patients at risk at the three time points are below the horizontal axis.

in which thromboembolic events may be directly attributable to chemotherapy or chemotherapy + TAM. Conversely, during the follow-up period, the patients in both treatment arms remained on treatment with TAM, a well-known pro-thrombotic drug. Again, no differences in the CVA incidence were observed.

Discussion

The present report is the first interim analysis of the GEICAM-9401 study. Median follow-up was 54 months but because the recruitment period was 5 years, the shortest follow-up period was 22 months while the longest was 83 months. Hence, the preliminary nature of part of our follow-up data should be kept in mind when interpreting the results of this trial. The magnitude of the difference on the 5-year DFS estimation was 5% (75% SEQ versus 70% CON) and the adjusted hazard ratio showed an 11% advantage in favor of SEQ. These results are statistically non-significant (log-rank $P = 0.43$ and hazard ratio 95% CI 0.71–1.73), and the obvious interpretation is that the trial does not provide evidence of superiority of one treatment arm over the other. However this interpretation denies any clinical value of the observed trend. A more careful review of the statistical data is in order in interpreting the results. The trial was planned to have an 80% power for detecting a 10% difference on 5-year DFS for an expected rate of 5-year DFS of 50%. As such, 724 patients were deemed necessary. Our actual recruitment and post-treatment number of patients that were evaluable was 474, in whom there was a lower than expected recurrence rate that resulted in a 5-year DFS of 70% and 75% (SEQ versus CON, respectively) and an observed 5-year DFS difference of 5%. The better-than-expected DFS may be interpreted as the result of the relative immaturity of the follow-up together with a selective over-representation of patients with good prognosis and, probably, historical improvement in staging process (stage migration known as the Will Rodgers phenomenon) [19]. The actual discriminatory power dropped to 35%. Clearly, this is an under-powered trial with a high probability of the statistically non-significant result being a false-negative. Failing to recognize a false-negative result may also have negative consequences. If the reality were that the SEQ protocol was superior, then those clinicians who opted for the CON schedule would be under-serving their patients. We acknowledge that it is highly debatable whether this statistically non-significant trend should be taken into account in the clinical decision-making process at all. If the results from the present trial were the only data available, then the challenging question would be whether the indication of a non-significant trend proceeding from an under-powered randomized trial is better than no data at all when choosing between CON and SEQ addition of TAM to the chemotherapy. We believe the inclination should be towards acceptance of the latter option because, in everyday clinical practice, this is an important decision and one which is often made on the basis of institution opinion and tradition rather than on objective data. Hence, weak evidence such as a statistically non-significant trend would be better than absolutely no evidence at all. This is a practical judgement inferred from our results which relies heavily on contextual circumstances (such as

Table 3. Cox proportional model including the treatment arm variable adjusted for the three statistically significant prognostic factors

Variable	β	*P* value	Hazard ratio (exp β)	95% CI for exp β	
				Lower	Upper
No. of metastatic nodes	0.022	0.006	1.022	1.006	1.038
Tumor size	1.025	0.004	2.786	1.379	5.628
Histology grade	0.845	0.001	2.329	1.484	3.656
Treatment arm	0.105	0.644	1.110	0.712	1.730

Categorical variables: arm (SEQ, 0/CON, 1); tumor size (T1, 0/>T2, 1); histology (grade 3, 1 or grade 2, 0).
CI, confidence interval; CON, concomitant; SEQ, sequential.

a biological rational, other trial results, and lack of any reason favoring the CON treatment arm), rather than a direct translation from our research results to clinical practice.

The findings from an equivalent trial (INT-0100) by Albain et al. [20] are controversial as well. Compared to the under-powered GEICAM trial, the INT is extensive and with protracted follow-up but the statistical aspect of the INT may be considered equivocal. This is because one-sided tests of significance were used despite the direction of the outcomes not being known and in which the two-sided tests are more appropriate. Further, the 95% CI of the adjusted hazard ratio included the unit 1. It may be argued that INT-0100 results constitute level I evidence and that they may be sufficient to warrant a change in clinical guidelines. In this setting, GEICAM-9401 results take on considerable importance because they confirm and extend the INT conclusions. Of considerable note is that the findings are consistent between both trials, i.e. the SEQ treatment scheme shows consistently better results than the CON scheme. The observations of DFS curves that are identical over the first 3 years but diverge subsequently to show an absolute difference of 5% at 5 years, of adjusted hazard ratios of 11% in GEICAM and 18% in INT are remarkable for their similarity in the two trials despite the differences in the chemotherapy regimens employed (epirubicin–cyclophosphamide in the GEICAM trial and CAF in the INT). Pooling the present data with that from the INT would probably improve the overall statistical significance and would strengthen the main conclusion which would be that of SEQ superiority. The credibility of these results is important for clinical practice and, should the recommendation be accepted in the oncology community, sequential administration should become the standard of care. For those clinical practitioners who may be concerned that TAM could lose part of its efficacy as a consequence of delaying its administration, the results from the French trial TAM-2 [21] provide reassurance with the demonstration that, even when administered after considerable delay in adjuvant therapy, TAM delivers a degree of clinical benefit.

From a perspective of the current study, the decision to include patients whose tumors were hormone receptor negative could be seen as inappropriate. It was a debatable, but conservative, decision at the time of the study design and was based on the published literature. The 1992 EBCTCG meta-analysis suggested a small but worthwhile benefit of TAM administration in hormone receptor negative patients. Moreover, the reduced cancer risk for the contralateral breast together with the reported benefits on skeleton (and possibly on cardiovascular risk) were considered as additional reasons to administer TAM to hormone receptor negative patients. It was in the 1998 update of the EBCTCG meta-analysis [22] that the futility of prescribing TAM for patients with hormone receptor negative tumors was stated. Whether the antagonism between TAM and anthracycline-containing regimens can be applied to cyclophosphamide, methotrexate and fluorouracil (CMF) regimens remains to be clarified. When designing our trial we chose an anthracycline-containing chemotherapy regimen because there were some theoretical reasons to expect synergism of action [5]. There were no equivalent considerations in support of CMF. The evidence supporting the value of adding CMF to TAM in postmenopausal patients with estrogen receptor positive tumors [12] was scarce at the time the present trial was inaugurated. A further consideration behind our choice of an anthracycline-containing chemotherapy was the reported incidence of thromboembolisms. The ECOG study [17] in postmenopausal women reported an incidence of venous events of 0.4%, 2.3% and 3.5–9.1% for observation alone, TAM, and combined TAM–chemotherapy groups, respectively. The corresponding values for arterial events were 1.7%, 1.2% and 0–1%, respectively. In contrast to these findings, the NSABP TAM + AC trial [23] reported an incidence of 2.3% for DVT and 0.8% for PE. These values were not very different from the observed incidence with TAM alone in the same trial, i.e. 0.8% and 0.8% for DVT and PE, respectively [23]. The Canadian–NCI trial [18] reported an incidence of thromboembolic events of 13.6% in the CMF + TAM combination compared to 2.6% for the TAM treatment arm alone. Our observation of an incidence of DVT + PE of 11 of 474 patients (2.32%) is closer to the NSABP TAM + AC trial than to the other reported studies. The incidence of stroke/CVA was four of 474 patients (0.84%) which was higher than the 0.22% expected incidence for TAM in healthy women aged >50 years [24], but well within the expected limits for postmenopausal breast cancer patients [17].

One of the most intriguing issues arising out of this trial is the biological mechanism underlying the observed results. The antagonism observed between TAM and chemotherapy is a clinical reality but the biological inter-relationship is far from clear. Certainly, those hypotheses predicting an additive or synergistic effect such as reversal of p170-mediated resistance to anthra-

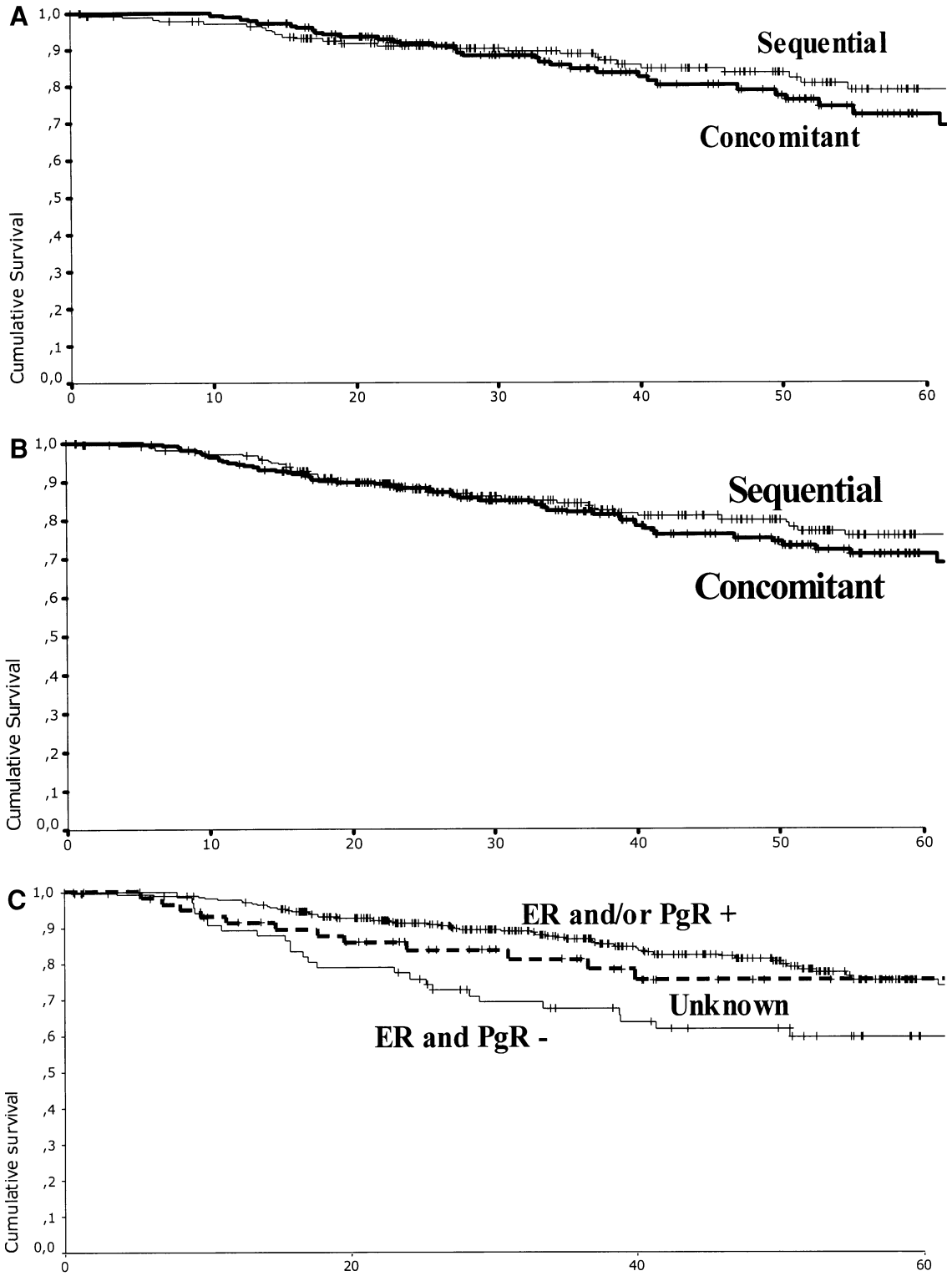

Figure 3. Kaplan–Meier plot of disease-free survival (DFS) in months segregated by hormone receptor status. (**A**) Estrogen receptor (ER) and progesterone receptor positive; (**B**) ER-negative or receptor status unknown; (**C**) the DFS plots by hormone receptor status, independent of treatment arm.

cyclines by TAM [25, 26], or calmodulin inhibition [27] can be rejected since they appear not to play a clinically relevant role, at least at the drug dose used in the present trial. Cytokinetic resistance to chemotherapy that may be induced by TAM could be the most plausible explanation for the observed results. TAM appears to modify the cell cycle transit and reduces the number of proliferating cells [28] and, thus, creates a cytokinetic resistance to chemotherapy [1, 5]. Consistent with this interpretation is the pattern of the DFS curves in which no interaction is apparent during the first 3-year period, i.e. patients with the quickest relapse

Table 4. Worst grade toxicities segregated with respect to treatment arm

Toxicity	Grade	Sequential arm		Concomitant arm	
		No. of patients	%	No. of patients	%
Hemoglobin	1–2	35	14.7	41	17.3
	3–4	0	0	1	0.4
Leukocytes	1–2	71	29.8	64	27.0
	3–4	2	0.8	2	0.8
Neutrophils	1–2	75	32.2	69	29.4
	3–4	20	8.4	12	5.2
Platelets	1–2	1	0.4	0	0
	3–4	3	1.3	3	1.3
Mucositis	1–2	91	39.1	96	41.2
	3–4	4	1.7	3	1.3
Diarrhea	1–2	22	9.3	17	7.3
	3–4	0	0	3	1.3
Emesis	1–2	147	62.0	141	60.3
	3–4	19	8.0	23	9.8
Hepatic	1–2	9	3.8	6	2.6
	3–4	0	0	2	0.9
Alopecia	1–2	19	8.1	23	9.9
	3–4	212	90.2	205	88.4

Table 5. Cardiovascular events segregated by treatment arm and during and post-chemotherapy phases

Event	Sequential arm (No. of patients)	Concomitant arm (No. of patients)
During chemotherapy		
Pericarditis; grade 1–2	0	1
Heart rate; grade 1–2	0	1
Heart function; grade 1–2	2	2
Forearm phlebitis	7	6
Deep vein thrombosis	1	4
Pulmonary embolism	1	0
Stroke	1	1
Post-chemotherapy		
Deep vein thrombosis (legs)	2	1
Pulmonary embolism	2	0
Stroke	1	1
Congestive heart disease	2	1

are, probably, TAM-resistant. However, the antagonism becomes apparent in patients with late relapse and represents, probably, patients who have TAM-sensitive tumors. Also, the slow-growing micro-metastases with stronger dependence on estrogens to maintain the pace of proliferation are, probably, more sensitive to the antiproliferation effect of TAM. Although it has been a well-documented laboratory phenomenon, our trial, together with the INT, is the first clinical evidence supporting this hypothesis in the adjuvant setting. The antagonism that a cytostatic agent such as TAM could exert on cytotoxic drugs should alert the clinical research community regarding the possibility of this interaction being a more general phenomenon. In the present era of new targeted drug development, some of them may work as cytostatic agents and, as such, the opportunity to use them in SEQ or CON schemes with chemotherapy should not be missed.

The cytokinetic hypothesis is not the only possible interpretation of the observed antagonism. Tamoxifen has other effects such as anti-angiogenic, cell-membrane perturbation of structure and function, as well as interaction with growth factors and signaling molecules [29]. Whether any of these pathways plays a role remains speculative.

Acknowledgements

This work has been supported by an unrestricted grant from Pharmacia Spain.

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