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Evolution of Adjuvant Chemotherapy for Breast Cancer: Review of Our Experience with Three Chemotherapy Regimens and Trastuzumab, Between 2000 and 2017

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Abstract

Background: Over the last decades, the standard adjuvant chemotherapy for breast cancer changed various times, following the results of randomized controlled trials. The aim of the present study was to review the experience of our Unit, comparing three different regimens for breast cancer, used in subsequent years: CMF, protocols containing anthracyclines, and then taxanes, either in monotherapy or in combination with anthracyclines and/or trastuzumab.

Methods: We retrospectively analysed the results of 230 breast cancer patients operated on in our Unit between the year 2000 and 2017 and treated with adjuvant chemotherapy. The patients had mean follow-up of 60 months (Range 12 months to 192 months). Disease-free survival and toxicity were evaluated according to the adjuvant chemotherapy regimen used.

Results: The chemotherapy regimen used significantly influenced disease-free survival (p=0.02). The impact on relapse appeared comparable choosing either CMF scheme or anthracyclines. Whereas, taxane-containing regimens proved to be significantly protective against relapse (HR=0.33), by univariate Cox analysis (p=0.04). By multivariate analysis, the influence of adjuvant chemotherapy was even stronger (p=0.01) and taxane reduced dramatically the relapse risk (HR=0.26). The adjuvant chemotherapy regimen was a significant and independent prognostic factor for disease-free interval. The superiority of taxane-based therapy, compared to anthracyclines and CMF, was evident also in triple-negative tumours, as 100% of patients were disease-free after 96 months of follow up. Concerning toxicity, taxane was the best tolerable regimen and significantly reduced hematological, gastrointestinal and cutaneous toxicity. In a separate analysis for HER2-positive tumours, 90% of the patients treated with trastuzumab were disease-free at 100 months follow up, in comparison with only 65% of HER2-positive women not undergoing this treatment.

Conclusions: Our study showed that taxane-containing regimens, either in combination with anthracyclines or in monotherapy, were the most effective and tolerable adjuvant chemotherapy for breast cancer. These results confirm the current literature knowledge about the effectiveness of taxanes as adjuvant treatment for breast cancer. In addition, our study also confirmed the value of trastuzumab as adjuvant therapy in HER2-positive women on disease-free survival.

Keywords: Breast cancer; Adjuvant chemotherapy; Taxanes; Anthracyclines; CMF; Trastuzumab; Toxicity

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Introduction

Chemotherapy has represented the first systemic adjuvant therapy for breast cancer and it was introduced in the 1970's. Since then, several randomized clinical trials aimed to compare polychemotherapy regimens and monochemotherapy and the results are collected in periodic meta-analysis by EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Currently we know that, when chemotherapy is indicated after surgery, polychemotherapy is preferable as compared to a monotherapy, because of its superiority in terms of overall survival and disease-free survival [1].

It is possible to classify schematically three different generations of adjuvant chemotherapy regimens for breast cancer with progressive better results as regards outcomes like disease-free interval and overall survival [2]:

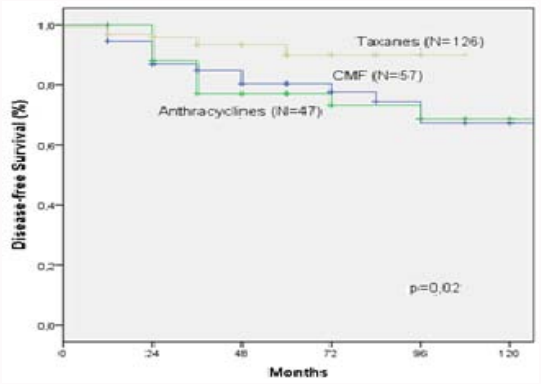

Figure 1: Kaplan-Meier Estimate of Disease-free Survival, choosing different adjuvant protocols.

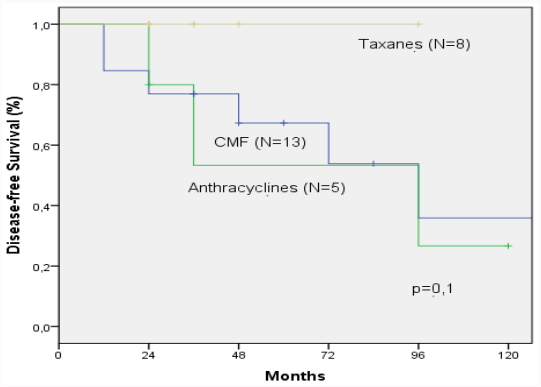

Figure 2: Kaplan-Meier Estimate of Disease-free Survival, choosing different adjuvant protocols, in triple negative tumours subgroup.

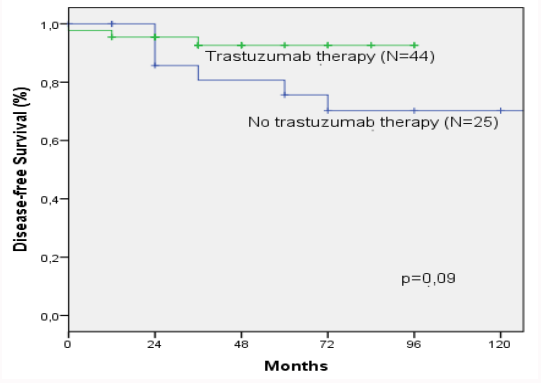

Figure 3: Kaplan-Meier Estimate of Disease-free Survival in HER2-positive patients undergoing trastuzumab or not.

- First-generation regimens: these mainly consists in CMF protocol (6 cycles to 12 cycles), a combination of cyclophosphamide, methotrexate and fluorouracil. This scheme is nowadays rarely used.

- Second-generation regimens: anthracyclines reduced mortality of 16% and risk of relapse of 11%, compared to CMF [2]. These regimens have an important toxicity, in particular cardiac (heart failure) and hematological (acute myeloid leukaemia) toxicities [3].

- Third-generation regimens: protocols containing either both anthracyclines and taxanes or taxanes in monotherapy. These schemes were introduced between 1990 and 2000 and reduced mortality of 14% and risk of relapse of 16% as compared to second-generation regimens. They are given both in combined (TAC/TEC) and sequential (AC/EC/FEC x 3-4 cycles followed by taxanes) schemes.

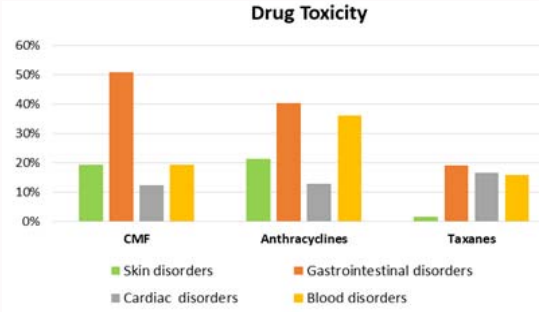

Figure 4: Drug-related main toxic effects due to different adjuvant chemotherapy.

In tumours positive for HER2 (Human Epidermal Growth Factor Receptor 2), a one-year-long therapy (18 cycles) with recombined humanized monoclonal antibody trastuzumab is indicated [4-7]. If trastuzumab is given in combination with anthracyclines, it is necessary to monitor carefully and periodically cardiac function, because of the additional cardiac toxicity. However, the effect on heart of this antibody appears to be reversible, in literature studies [8].

The aim of the present study was to analyse the results in our unit between the years 2000 and 2017, comparing three different eras of adjuvant chemotherapy regimens for breast cancer: CMF regimen, anthracyclines-containing regimens, and taxanes either in monotherapy or in combination with anthracyclines and/or trastuzumab.

Materials and Methods

We collected data of all patients operated on for invasive breast cancer and subsequently treated with adjuvant chemotherapy at our breast unit, between the year 2000 and 2017. As the chemotherapy regimen varied with time, we had the opportunity to compare the results of different protocols. The patients were followed for an average 60-months (Range 12 months to 192 months) with clinical breast examination every 6 months, mammography and breast ultrasound every 12 months. Any relapse (local, regional or distant) and disease-related death was recorded. We focused our attention on disease-free survival and toxicity. Overall, we had 230 patients with adequate follow up available. In addition, we identified two subgroups of patients: 69 women had HER2 positive tumors and 26 patients with triple-negative tumours.

All the patients included in this analysis received adjuvant chemotherapy for a number of cycles adequate for each scheme. The patients received the following drugs and protocols: epirubicin and doxorubicin (anthracyclines), paclitaxel and docetaxel (taxanes), cyclophosphamide, vinorelbine, AC, TC, TCH, EC, CMF, and FEC.

Between two cycles of chemotherapy, each patient was checked by clinical examination and blood tests. Furthermore, cardiac function was regularly monitored by electrocardiography and echocardiography, because of the possible cardiac toxicity of some of these therapeutic regimens.

Toxicity was graded in accordance with the Common

Terminology Criteria for Adverse Events version 4.0 and only grade 3 to 4 events were considered in the subsequent analysis [9].

Disease-free survival was estimated by Kaplan-Meier method and the significance of the differences were evaluated by Log-Rank Test. Univariate and multivariate Cox analyses were performed to estimate the significance of the correlation among all the parameters in the study with regard to disease-free survival. All statistics were carried out with IBM SPSS for Windows, Version 20.

Results and Discussion

In the whole series of 230 patients, 57 women were treated with CMF scheme, 47 were given anthracyclines and 126 received taxanes either in monotherapy or in combination with anthracyclines. In addition, among the 69 patients with tumor positive for HER2 receptor, 44 received monoclonal trastuzumab for 12 months, whereas 25 patients did not. Overall, the mean disease-free interval was 55 months, (Range 12 months to 192 months).

Disease-free survival was significantly higher in the taxanes group, as compared with CMF protocol and anthracyclines in monotherapy (p=0.02). After 100 months of follow up, roughly 63% of women treated with CMF or anthracyclines were free from disease, in comparison with 90% for patients receiving taxanes in monotherapy or in combination with anthracyclines (Figure 1). Taxanes proved to be particularly effective in the subpopulation with triple-negative tumours. In this sub-group 100% of patients were disease-free after 96 months, vs. 50% of women receiving CMF or pure anthracyclines schemes (Figure 2). However, because of the limited number of patients, this result did not reach statistical significance (p=0.1).

In the sub-group of HER2-positive patients, 90% of women receiving trastuzumab were free from recurrence after 96 months of follow up, vs. 65% for the patients not receiving trastuzumab. Again, this striking difference did not reach the level of statistical significance because of the small sample in analysis (Figure 3).

By univariate Cox analysis, taxanes proved to be significantly protective against relapse (HR=0.33; p=0.04). Whereas, the impact on recurrence appeared to be comparable choosing either CMF scheme or anthracyclines (Table 1). By multivariate analysis, only three parameters resulted significant and independent predictors of recurrence: stage AJCC, type of adjuvant chemotherapy and triple negative tumours (Table 2). The superiority of protocols including taxanes in reducing the recurrence risk was even stronger when assessed in the multivariate model (HR=0.26; p=0.01). Therefore, the type of adjuvant chemotherapy turned out to be a significant and independent prognostic factor.

Concerning chemotherapy-related toxicity, among patients receiving the CMF scheme, the most frequent events were gastrointestinal (50.9%), cutaneous (mainly alopecia, 19.3%) and haematological (19.3%). Anthracyclines primarily caused gastrointestinal (40.4%), haematological (36.2%), cutaneous (21.3%) and cardiac (12.8%) toxic effects. Taxanes showed significantly lower toxicity, in particular as regards haematological (15.9%), gastrointestinal (19%) and cutaneous (alopecia, 1.6%) events (p<0.001) (Figure 4).

In the current study, reviewing our unit experience with adjuvant chemotherapy for breast cancer, we compared the results of three classic protocols that represented the standard in subsequent years: CMF, anthracyclines and then taxanes, in most recent years. This

Table 1: Univariate Cox analysis for disease-free survival, choosing three different adjuvant protocols.

(p=0.04)	Disease-free Interval
	HR
CMF Scheme	Ref.
Anthracyclines Regimens	0.89
Taxanes Regimens	0.33

Table 2: Multivariate Cox analysis for disease-free survival, considering the interaction among three independent prognostic factors.

		Disease-Free Interval	
		HR	p
AJCC Stage	Stage 1	Ref.	0.002
	Stage 2	1.64	
	Stage 3	5.15	
Adjuvant Chemotherapy	CMF	Ref.	0.01
	Anthracyclines	0.88	
	Taxanes	0.26	
Triple Negative Tumours	Not Triple Negative Tumour	Ref.	0.03
	Triple Negative Tumour	2.5	

is a retrospective analysis and it has the obvious limitation of this study design. Nonetheless, we found that patients receiving taxanes-containing regimens had a significantly better Disease-free survival (Figure 1). In addition, either by univariate or by multivariate Cox analysis, adjuvant treatment containing taxanes was associated with a significant reduction of recurrence risk. In particular, by multivariate Cox analysis we found that taxanes as adjuvant were associated with roughly a four-fold decrease of recurrence risk, as compared with the other regimens (HR=0.26; p=0.01). In addition, by multivariate analysis it was possible to assess that the type of adjuvant chemotherapy administered was a significant and independent prognostic factor in the current series. These results are in accordance with currently literature knowledge about effectiveness of taxanes in the adjuvant setting [2]. Recently, Watanabe et al., [10] reported results of a randomized clinical trial, which compared taxanes in monotherapy with a combination of taxanes and anthracyclines as adjuvant chemotherapy in women affected by breast cancer with lymph node involvement. In this specific subgroup of mammalian tumours, it was not possible to demonstrate taxanes monotherapy non-inferiority, so the association of anthracyclines use is still mandatory in this group of high risk patients [10]. Therefore, it is possible to state that combination of anthracyclines and taxanes is currently the most effective adjuvant chemotherapy for breast cancer. In addition, it was interesting to analyse disease-free survival according to type of chemotherapy treatment in the subgroup of triple negative tumours. Women with these tumours frequently have an unfavorable prognosis, firstly because of the lack of specific therapeutic tools to treat them, as pointed out by Sledge et al., [11] Furthermore, triple negative tumours often occur in premenopausal women and show aggressive behavior. At present, there is increasing interest for systemic platinum chemotherapy as treatment for these tumours [11]. We don't have Platinum treated patients in this series. However, in our experience we found a benefit in using taxanes in triple negative tumours in comparison with former schemes: 100% of taxane-treated women were free from recurrence vs. 50% of patients who received CMF or anthracyclines, after 96-months follow-

up. Because of the limited number of patients with triple negative tumours in this analysis, our results were not statistically significant and the striking difference observed has to be interpreted with caution. It is interesting, however, that our findings are in accordance with data reported in a review of Whaba et al., [12] which focused on this specific issue.

It is also relevant that the known effectiveness of adjuvant therapy with trastuzumab, in HER2-positive tumours was confirmed in our data set [4,5,13]. Indeed, we found that 90% of women who received Trastuzumab were free from disease vs. 65% of patients not treated, after 96-months follow-up. Again, these results were not statistically significant because of the limited number of HER2-positive patients in our sample (Figure 3). Nonetheless, it is interesting to observe how, in the clinical practice, the introduction of Trastuzumab in more recent years has dramatically influenced the outcome of the patients with HER-2 positive breast cancer, even in our relatively small series.

With regard to toxic effects, in the current study taxanes allowed to reduce significantly gastrointestinal haematological and cutaneous toxicity, that occurred in 19%, 15.6% and 1.6%, of the patients, respectively, in comparison with CMF and pure anthracyclines regimens. Cardiac toxicity was, at a first glance, relatively high among patients receiving taxanes protocols (Figure 4). However, this possibly occurred because many patients in the taxanes group also received anthracyclines and trastuzumab. Therefore, it is likely that most of the cardiac toxicity events were due to these latter agents. Actually, anthracyclines cause important toxic effects, mainly haematological, gastrointestinal, cardiac and cutaneous (alopecia).

Conclusion

The review of our experience in adjuvant chemotherapy for breast cancer showed that the introduction of taxanes-containing protocols turned out to be safer and more effective in increasing disease-free survival. Therefore, our data in agreement with current literature knowledge, confirm that taxanes containing regimens, generally in combination with anthracyclines, should be considered the first choice chemotherapy in the adjuvant setting for breast cancer. In future studies it will be interesting to test the effectiveness of pure taxanes chemotherapy. Possibly this schedule could produce even greater safety with equal efficacy. Currently such studies are ongoing, as reported by Watanabe.

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