



# Selecting chemotherapy schedules for adjuvant treatment of early stage breast cancer, what is the rationale behind?

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### ABSTRACT

Breast cancer is one of the most prevalent cancers that oncologists are faced with in their clinics. The varieties of clinical features of the disease result to very different scenarios in the processes of treatment decision making. While classic factors of stage, grade, age and hormone receptor status are still the criterion for choosing treatment, a very delicate list of other prognostic and predictive factors have been entered to this field over recent two decades. The evidence-based medicine rules to treat patients based on the best evidences that have been found by powered randomized clinical trials. Different panels and guidelines gathering these evidences try to help oncologists to find the best treatment methods through the variable and sometimes contradicting results. As it is always the main objective, increasing the survival rates in addition to the ideal aim of curing the disease is usually the target. Finding the best and the most practical chemotherapy regimen against breast cancer needs to notice the biology of this disease and its varieties along with each individual patient condition. It is clear that not all patients need the most complicated and expensive treatment.

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## Introduction

As variability of adjuvant chemotherapy regimens is developing day to day, efficacy is the pivotal point and driving force for innovation of newer regimens. This can translate into decreased mortality and recurrence of breast cancer. Although some relatively exact and quantitative molecular method exist for the selection of the other modalities of systemic therapies such as hormone therapy and targeted therapy, more general and conventional factors such as size of the tumor, lymph node status and the patients' health consideration are used for the selection of chemotherapy regimens.

There are many studies that emphasize the benefits of chemotherapy for both node positive and node negative, hormone receptor positive and

hormone receptor negative patients regardless of age and menopausal status. Nevertheless, all these coming studies pay less attention to overall gain of chemotherapy. The concept of absolute benefit is worth attention to this particular topic. This means when a study shows statistically significant benefit of a chemotherapy regimen, actually there may exist a little variety from the viewpoint of the rates of recurrence or death between different groups of patients. This issue can be related to the overall low recurrence rate of disease, due to the natural behavior of disease, the very early stage of disease or the interventional influence of other factors such as the chemotherapy-induced amenorrhea and the hormonal effect. It is more complicated to select an

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appropriate chemotherapy regimen when the molecular factors such as the rate of hormone receptors positivity, HER2/neu receptor status and histological grade in addition to other clinicopathological factors are the base for decision making. Cases in whom the gain of chemotherapy is moderate or in other words the absolute benefit of therapy is low, the patient preference and the complications of treatment are more important to select the chemotherapy regimen. This is the reason why in patients with cardiac disease and neuropathic disease, anthracyclines and taxanes are not preferred treatments, respectively.

Currently, there is a group of patients that, based on the screening, increasing attention and general knowledge of breast cancer; their tumor is discovered in very early stages and with low growth indexes and high probability of being hormone responsive based on the screening, increasing attention and general knowledge of breast cancer. Chemotherapy in these low risk patients has low absolute benefit. Thus, patients not only will not be helped significantly by chemotherapy but also will be harmed by its complications and toxicities.

### **Background adjuvant chemotherapy studies**

Initial studies of adjuvant chemotherapy were organized on high risk lymph node positive patients, however, subsequent studies also emphasized on the benefit of adjuvant chemotherapy in lower risk node negative patients.

According to the Oxford overview:

1. Fifteen years follow-up of patients established advantages of chemotherapy regardless of age, hormone receptor status and receiving the adjuvant endocrine therapy.
2. Four to eight cycles of chemotherapy or six months of chemotherapy have more advantage than single cycle regimen.
3. This overview supporting many other individual studies that showed the superiority of anthracycline-based chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil (CMF) and other nonanthracycline-based chemotherapy(1-3).

About six months of chemotherapy with these regimens reduced the annual death rate due to the breast cancer by 38% in women less than 50 and 20% in those 50 to 69 years of age. It means that the absolute benefit in women younger than 50 is 12.3% reduction in recurrence and 10% reduction in death and in women with 50 to 69 years old, this is 4.1% reduction in recurrence and 3% reduction in death. In all of these trials, the number of women over 70 years was not enough to achieve reliably distinctive result of chemotherapy survival benefit. As mentioned earlier, these effects are largely inde-

pendent of hormone receptor status and the use of tamoxifen, nodal status and other properties of tumor. Indirect comparison between adriamycin and epirubicin containing regimens showed no statistically reliable differences in advantage of any drug.

While CMF regimen largely has been substituted with other protocols nowadays, it seems that there are many different options for chemotherapy of node positive breast cancer patients(4). However, very few numbers of these regimens have been compared together in a controlled clinical trial. Thus, selection of the best treatment is obscure and as a result, there are broad-spectrum standards of therapy in USA, Europe and Canada (5-8).

### **Epirubicin rather than doxorubicin**

The EBCTCG meta-analysis showed that about six cycles of anthracycline containing regimens significantly increased the survival rate compared to oral CMF, however, most trials investigated the standard doses of anthracycline, did not show this superiority in disease free survival and overall survival(9).

On the other hand, many more trials such as The Cancer and Leukemia Group B (CALGB) 9344, CALGB 8541 and National Surgical Adjuvant Breast and Bowel Project (NSABBP) B22 established that increasing doses of doxorubicin did not lead to significant improvement in survival compared to standard doses(10-14).

Meanwhile, at least three studies that applied escalated doses of epirubicin regimens, the Belgian Study (15,16), the National Cancer Institute of Canada MAS (17,18) study and the French Adjuvant Study Group (FASG) 05 (19,20) demonstrated increasing in survival rates whereas one small study that compared high doses of epirubicin with CMF did not achieve a same conclusion in high risk premenopausal patients (21).

In spite of the fact that equimolar doses of these two drugs act similarly in advanced diseases, higher doses of epirubicin have better outcome than standard dose of anthracycline regimen and escalated doses of doxorubicin regimen in adjuvant setting. To make a point, it may conclude that epirubicin is more preferred in adjuvant setting compared to doxorubicin at escalated doses.

### **Taxanes: an important stepping forward**

Introduction of taxanes is an important progression in the treatment of early stage breast cancer. CALGB 9344 was the first randomized clinical trial showing that sequential addition of paclitaxel following 4 cycles of adriamycin/cyclophosphamide (AC), improved both overall survival (OS) and disease free survival (DFS) in node positive patients. It should be noted that although a consistent benefit was observed, the resulting absolute benefit of

2-4% was not very great. This means that approximately 35 to 45 patients need to be treated for one to benefit (12). Therefore, physicians should consider toxicity, complications and the cost of treatment in addition to the survival advantages at the time of prescription of taxanes. In a pooled analysis including 15300 patients, the benefit of taxanes was present, whether prescribe sequential or concurrent, and there was no difference at the matter of superiority of one taxane on the other one in a subanalysis. Nevertheless, docetaxel had a better influence on OS than paclitaxel in a smaller and not powered study (9,22).

This amount of absolute benefit of adding taxanes in adjuvant setting is approximately at the same value that EBCTCG meta-analysis showed that it was pertaining to anthracyclines benefit and established them as gold standard of treatment in the breast cancer adjuvant therapy.

It has been assumed that administration of cycles in shorter courses was more effective than dose escalation. Based on this assumption, CALGB 9741 trial compared AC followed by paclitaxel every 3 weeks with the same regimen and the same doses that administered every 2 weeks among 2000 patients. They demonstrated that the every 2-week regimen led to improvement in survival and reduction of recurrence. In this study, AC followed by paclitaxel was compared to sequential doxorubicin/paclitaxel/cyclophosphamide (that each drug administered after completion of scheduled dose of prior drug) and they showed that there was no difference between them (23).

In a neoadjuvant study, it has been demonstrated that weekly paclitaxel was better than every 3-week paclitaxel in terms of complete pathologic response (4).

Furthermore, based on ECOG 1199 trial that compared 4 different types of taxane regimens including weekly paclitaxel, 3-week paclitaxel, weekly docetaxel and 3-week docetaxel after four cycles AC in adjuvant setting, weekly paclitaxel had better outcome compared with 3-week paclitaxel. There was not any significant advantage on OS in weekly paclitaxel versus 3-week administration of docetaxel. However, these two treatment had different side effects. Weekly paclitaxel had more neuropathy whereas 3-weekly docetaxel had more febrile neutropenia (24).

NSABBP 30 trial compared sequential AC followed by docetaxel with four cycles of docetaxel/doxorubicin/cyclophosphamide (TAC) in node positive breast cancer. They concluded that sequential AC/docetaxel was better than 4 cycles of TAC regimen and four cycles docetaxel/cyclophosphamide (DC) was not merely enough for node positive breast cancer (25).

A discussion has emerged the question of the benefit of taxanes in estrogen receptor (ER) negative tumors. However, it is believed that both groups of

ER positive and ER negative tumors benefit from adding taxanes to chemotherapy protocol. Moreover, the absolute benefit of ER positive tumors is larger (24).

Meanwhile in a trial including 3171 node negative breast cancer patients and comparing four or six cycles of either AC or paclitaxel, there was not any advantage of prolonging treatment from 4 cycles of AC or paclitaxel to 6 cycles of the same regimen (26).

### ***Dose dense regimen***

As it was introduced in 2003 by Citron et al., the dose dense regimen of AC-Paclitaxel every 2 weeks supporting by Granulocyte-colony stimulating factor (GCSF) has been one of the most interesting regimens of adjuvant chemotherapy of high risk early stage breast cancer (22). This increased benefit have been criticized to be specific with hormone-receptor negative tumors, high proliferative index tumors and tumors with overexpression of HER2 (27). Considering the requirement of bone marrow supportive agents (e.g. GCSF) in dose dense regimens and long-term risk of increasing the probability of myelodysplastic syndromes, it seems that utilization of two-week AC regimen following by weekly paclitaxel is better than dose dense schedule when prescription of taxane-base regimen is necessary (28).

### ***Can we abandon anthracycline for early breast cancer?***

Considering the potential hazards of anthracycline utilization in early stage of breast cancer, its elimination from treatment protocols has been a matter of attention. Historical alternative is CMF that was shown to be comparable to AC (29).

US oncology research trial 9735 that performed on 1016 patients showed the increasing of DFS and OS in node negative or 1-3 node positive patients with 4 cycles of DC in comparison with 4 cycles of AC (30). Nevertheless, the problem was that a four-cycle AC regimen was not appropriate for comparison in high risk patients and as previously discussed it had no superiority over CMF.

A group of node negative patients, including 2699 cases with tumor size more than 2 cm, HER2 negative or low S-phase fraction were assigned into two arms of CMF and cyclophosphamide, doxorubicin, and fluorouracil (CAF) with or without tamoxifen. Ten-year estimation indicated that CAF was not considerably better than CMF in terms of DFS, but it was slightly better in OS. Authors concluded that it could not be considered superior to CMF according to the higher toxicity of CAF (31).

### ***HER2 status as a predictor of response to adjuvant anthracycline therapy for early stage breast cancer***

During recent years, there have been many ret-

rospective studies that considered a connection between anthracyclines activity and HER2 status. One of these studies that was reported by the National Cancer Institute of Canada (2006) besides other trials confirmed the benefit of anthracyclines among patients with overexpression of HER2/neu receptor, while in HER2/neu nonamplified tumors; anthracyclines was associated with no clinical benefit (32).

Applying the results of these studies should be done cautiously in specific clinical fields such as triple negative tumors with a basal-like phenotype that frequently have BRCA1 mutation. Because molecular predictors of response to anthracyclines including topoisomerase II protein overexpression and DNA repair dysfunction are not limited to HER2 positive tumors and some of HER2 negative patients may also gain same clinical benefit from these agents (33).

Another study demonstrated that upper doses of doxorubicine did not have more effectiveness in HER2 positive status, but there was an obvious relationship between HER2 positivity and the benefit of adding paclitaxel to chemotherapy regimen after AC. Meanwhile for estrogen-receptor (ER) positive but HER2 negative tumors, there was no advantage of adding paclitaxel (34). The analysis of BCIRG 001 trial also showed a strong treatment effect of TAC regimen compared to FAC in HER2 positive patients (35).

### **Estrogen receptor status**

ER status has been considered to be an index of response to chemotherapy protocols. Once chemotherapy was recruited for breast cancer, only ER negative or unknown tumors were initially candidate for chemotherapy. However, it was then proven that even ER positive patients benefited from chemotherapy independent of tamoxifen, not as substantial as their ER negative counterparts did. It is true that more improvement is seen from adding new chemotherapy protocols such as dose dense regimen and drugs such as taxanes in ER negative tumors. In addition, tumors with high levels of ERs tend to be more responsive to hormone therapy than chemotherapy. Moreover, more complete pathologic response is seen in ER negative tumors in neoadjuvant setting. Based on these findings, some authors believe that ER status can affect adjuvant chemotherapy outcomes. However, meta-analysis by EBCTCG could not come to this conclusion and they did not show any effect of ER status on proportional risk reduction of adjuvant chemotherapy. We know that ER positive tumors are very heterogeneous. Based on the breast cancer molecular classification, groups of luminal A and B are both ER positive. In addition, the level of ER expression is different among these groups and it is waiting yet to precisely define which level of expression is the best threshold of chemosensitivity.

The 21-gene recurrence score (Oncotype Dx), in addition to its prognostic role in node negative ER positive patients may has a predictive role in forecasting benefits of CMF regimen. ER positive, lymph node negative tumors with higher score significantly benefit from adding chemotherapy to tamoxifen.

By the way, in ER positive patients, there are no benefits of higher doses of doxorubicine. Moreover, no significant advantages have been obtained applying more intensive regimens such as two-week AC/T in these groups of patients (4).

### **Toxicity**

The boundary of therapeutic and toxic effects of adjuvant chemotherapy is very narrow. In recent review of CALGB trial from 1985 to 2005, 0.7 % to 1.5 % of patients suffered from lethal complications and toxicities depending on age.

Apparently, healthy older patients are more likely to have grade four hematologic toxicity, discontinue treatment and dye due to acute myeloid leukemia/myelodysplastic syndrome (AML/MDS)(36).

Neuropathic complications, neutropenic fever, cardiac toxicity and AML/MDS are observed more frequently in 6 cycles of AC or paclitaxel than 4 cycles of the same regimen.

AML/MDS are observed exclusively in anthracycline-based chemotherapies particularly with epirubicin more than nonepirubicin-base regimen (19). However, 0.02% yearly increased in cases treated with these regimens is negligible compared to 0.01% in nonanthracycline-based regimens based on Oxford trial (2).

Neutropenic fever and infection occurs frequently using TAC and dose dense regimens that explain the necessity of GCSF prophylactic prescription (37).

There is close relation between cardiotoxicity and increasing doses of anthracycline particularly as combined with paclitaxel. Nonhematologic complications such as stomatitis, mucositis, hypersensitivity reactions, neurotoxicity and asthenia occurs frequently by escalated doses of anthracyclines and TAC regimen (37,38).

Finally, treatment costs including chemotherapy protocol, numerous transports and supportive cares are the different points in the prescription of various regimens; there are some examples: FFC 3370\$, AC60-T175 4340\$, CEF 4852\$, AC60-T225 5665\$, TAC 8266\$, dose dense 11741\$ (10,39).

### **Conclusion**

It seems that epirubicin, which is as effective as adriamycin from the view of improving survival rates, in escalating doses, have a better profile to include in chemotherapy regimen of breast cancer as far as an anthracycline is necessary to prescribe. Taxanes are cornerstone of treatment protocols

especially in high risk diseases and her2 positive ones and taxanes have positive effect on improving the survival independent from any prognostic factors. Although dose dense regimen has turn to be a standard treatment in subtypes of breast cancer from the view of toxicity and cost, two-week AC followed by weekly paclitaxel seems more interested. Tendency to abandon anthracycline-based regimens may be fulfilled with CMF in some type of breast cancers but this is not a widespread agreement. Her2 positive diseases consistently should not deprive of anthracyclines. The last but not the least matter of attention is the toxicity profiles and cost benefit of treatments which are among the other aforementioned factors that oncologists cannot decide to behave all over the early stage breast cancer diseases with almost the identical scenarios.

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### Conflict of Interest

The authors declare no conflict of interest.

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