

Anthracycline pretreated patients: who is who in the chemotherapy choice of relapsed breast cancer?

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Summary

During the last years, a strong trend towards excluding anthracyclines from the first-line chemotherapy (CT) of relapsed breast cancer (RBC) has been noticed. This trend is based on the concept of previous exposure of the tumor on the same drugs in the adjuvant setting. Consequently, some guidelines and experts recommend the avoidance of using these compounds for RBC under those circumstances, while the taxanes became the first treatment option. This article gives detailed references about the lack of correlation between the type of adjuvant chemotherapy (includ-

ing anthracyclines), and the clinical outcome of patients treated with front-line anthracyclines for RBC. It also addresses the weakness of this rationale based on recent translational research data and comments on the fact that anthracyclines could represent the best treatment option for some subcategories of patients with RBC. Concluding, this new trend seems more empirical than evidence-based, and clarification of this issue is warranted.

Key words: anthracycline pretreated, relapsed breast cancer, treatment choice

Defining the problem

Systemic treatment of RBC represents a great challenge for all medical oncologists. Despite substantial advances made in the field of chemo-, hormono- and targeted therapy, all the clinicians involved in this area still have to face a lot of unsolved issues in order to select the best treatment option. In the era of tumor gene profile identification [1,2] and targeted therapies [3], it seems rather surprising to find nowadays, in the controversial area regarding CT, aspects such as optimal duration of CT [4] or the role of single agents in the treatment of

advanced disease [5]. On the other hand, those aspects point to the fact that, maybe, we are too rushed to build new approaches without having solid ground to stand on. Leaving aside other important issues of the systemic treatment in RBC (the goal of systemic therapy, the role of hormonal therapy, trastuzumab and HER amplification, etc), we shall focus this debate on the CT strategy only, bearing in mind the optimum candidate for such an approach, i.e. hormone receptor-negative tumor, unfavorable clinical scenario, with or without Her2/neu overexpression/amplification [6].

For more than 20 years anthracycline-based CT represented the cornerstone of CT treatment for metastatic breast cancer [7]. Starting in the late 1990s, when the taxanes showed similar antitumor activity, both anthracyclines and taxanes, in combination or sequentially, became the standard of care in this setting [8]. In the same time, powerful metaanalyses showed that anthracycline-based adjuvant CT was associated with a significant reduction in the annual odds of relapse and mortality compared with cyclophosphamide/methotrexate/fluorouracil (CMF) [9,10]. Consequently, anthracycline-based adjuvant CT became universally accepted as a standard recommendation, while the

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CMF option was restricted to a limited category of patients [11]. On the other hand, neoadjuvant CT with anthracyclines proved that it could enhance the rate of conservative surgery, without any negative influence on patients' outcome [12]. As a result, the majority of the patients seen at the time of relapse have already been exposed to anthracycline-based CT. Accordingly, some guidelines [13] recommend that in advanced breast cancer the treatment choice should be made taking into account the previously given adjuvant CT. Moreover, some important references explicitly counsel that after adjuvant anthracycline treatment, this group of compounds should not be used in advanced disease in any CT-line, with first-line taxane being the most appropriate choice of this condition [6,14]. More confusing becomes the evaluation and the significance of the randomized trials promoting alternatives for first- or second-line treatments. A variety of terms have been used to describe the patients' status regarding the position of anthracyclines in their therapeutic history, which have never been properly defined. Therefore, one can find terms such as previous anthracycline exposure, anthracycline-pretreated, anthracycline-refractory, anthracycline-resistant, anthracycline failure, etc. The empiric explanation for skipping the anthracycline treatment if previously administered is the fact that resistant cells might have been selected during the previous exposure. While for patients with metastatic breast cancer progressing after first-line anthracycline-containing regimens the relation between tumor sensitivity and drug action could be considered more consistent (i.e. the tumor cells became anthracycline-resistant), in the case of neoadjuvant treatments this aspect might not be true.

Evidence supporting the response of solid tumors to the same agent after previous exposure in the metastatic or adjuvant setting

Various metastatic solid tumors, which have responded or remain stable for various periods of time to a given drug combination, can still be responsive to the same combination on a second challenge. It is the case of ovarian or small-cell lung cancer when salvage CT could be similar to the induction schedule, provided the progression-free interval (PFI) is longer than 6 [15,16] or 3 months, respectively [17]. The longer the PFI, the higher the chance for response. One can speculate that the PFI could represent a surrogate for the response rate at relapse. At this point it should be noted that most of the relapses for breast cancer treated with adjuvant CT appear after a minimum of 18-24 months [18].

Besides, the disease-free interval has been recognised as a major guiding factor helping the choice of proper CT for advanced breast cancer [19].

Pivotal drugs of adjuvant CT are not excluded from the CT combination at the time of relapse. For colorectal cancer, 5-fluorouracil is considered essential for both adjuvant and treatment of metastatic disease. Randomized trials have shown that upfront use of a new compound with a different mechanism of action (irinotecan) gives a poorer result than standard fluorouracil/leucovorin (FUFOL) CT [20]. In ovarian cancer, platinum compounds (and taxanes) are used for the treatment of relapse, regardless of their previous use in the adjuvant setting [21].

An important aspect which should be stressed in this context is the influence of adjuvant CT on the natural history of breast cancer. The EBCTG metaanalysis, evaluating the impact of adjuvant CT, showed that the benefit was greater for the disease-free interval than for overall survival (OS) (annual risk reduction 24 *versus* 15%) [10]. There are some experts who consider that adjuvant CT acts more in delaying the relapse than in eradicating the micrometastases [18]. Moreover, some reports point to the fact that adjuvant CT, whether this is CMF or anthracycline-based, has a negative impact on disease progression and response to therapy at the moment of relapse [22,23]. Ahman et al. [23] performed a retrospective analysis on 179 patients treated with adjuvant anthracycline *versus* 202 patients with no adjuvant treatment. Median survival (18 *versus* 28 months, $p < 0.001$) and response rate (RR-38 *versus* 69%, $p=0.001$), considered after disease relapse, were statistically significantly lower following adjuvant CT. The authors concluded that, while on the whole, adjuvant CT positively impacts disease-free (DFS) and OS, for relapsed patients previous exposure to CT contributes to a more aggressive course of the disease.

Does the type of adjuvant CT influence the outcome of patients treated for relapsed breast cancer?

The answer to this crucial question is of paramount importance to the issue brought into discussion. As for CMF, two studies suggest that its use in the adjuvant setting does not compromise the outcome of patients treated with the same schedule at relapse (Table 1) [24,25].

Both authors concluded that the RR was similar with that of patients not receiving adjuvant CT, and CMF should not be avoided in RBC if previously used for this condition.

Table 1. Prognostic factors and response rate for patients treated with CMF in the adjuvant setting and for relapsed disease

<i>Authors</i>	<i>Pts, n</i>	<i>RR (%)</i>	<i>Predictors for survival</i>	<i>p-value</i>
Gerritsen et al. [24]	47	30	Menopausal status	NS
			ER	NS
			Previous HT	NS
Castiglione-Gertsch et al. [25]	87	55	<i>Predictors for response</i>	
			Site of metastatic spread:	
			soft tissue (69%) vs. visceral (20%) Number of metastatic sites	< 0.05

Pts: patients; RR: response rate; HT: hormonotherapy; NS: not statistically significant

Venturini et al. [26] evaluated the influence of adjuvant CT, with or without anthracyclines, on the RR, time to progression, and median survival (MS), in 326 patients with RBC, while receiving epirubicin-based first-line treatment (epirubicin/cyclophosphamide/fluorouracil- FEC). The global RR was 50%, with a significant difference between patients who received *versus* those who did not receive adjuvant CT (43 *versus* 58%, $p=0.02$). On the other hand, there was no difference in the RR regarding the type of adjuvant CT: 43% for CMF *versus* 44% for anthracycline-based. MS was longer for patients without adjuvant CT (21.1 months) but similar to those who received adjuvant CMF (15.3 months) or anthracyclines (15.8 months). Multivariate analysis showed that adjuvant CT, in general, had a negative impact on RR and MS, but whether it was CMF or anthracycline-based, did not influence the efficacy of FEC as front-line treatment. Gennari et al. [27] evaluated the efficacy of first-line epirubicin /paclitaxel combination in 291 patients enrolled in 5 clinical trials. The global RR was 66%. No significant differences in RR, complete remission, time to tumor progression and MS were recorded for patients treated with adjuvant CMF, anthracyclines or patients being chemo-naïve (Table 2).

The authors concluded that the efficacy of first-line epirubicin/paclitaxel combination is not influenced by adjuvant CT or its type.

No other evidence has been found to challenge the above mentioned conclusions.

According to the data available so far, I believe that the recommendation of excluding the anthracyclines from the front-line option of RBC, based on the fact that the tumor was previously exposed to the same drug in the adjuvant setting, is more empirical than evidence-based.

What other concerns could be raised by using anthracyclines in both adjuvant and metastatic setting?

The cumulative dose of anthracyclines, leading to an enhanced risk of cardiotoxicity, could represent an argument favoring the rationale of exclusion. If this might be true for doxorubicin, epirubicin has an accepted cumulative dose of at least 950 mg/m² [28]. Even if we use a high-dose adjuvant regimen like 6 cycles of FEC, with epirubicin 100 mg/m² per cycle [29], we could still benefit from at least 4 cycles of epirubicin 75 mg/m² at relapse. Some other opinions could raise the issue of multidrug resistance protein (MDR1) which might be induced by previous exposure to anthracyclines. In this regard it is worth noting that some studies did not find any correlation between MDR1 expression and anthracycline exposure [30],

Table 2. Response rate and survival data for RBC patients treated with epirubicin /paclitaxel combination in relation to previous adjuvant CT regimen [27]

<i>Adjuvant CT</i>	<i>Pts, n</i>	<i>RR (%)^a</i>	<i>CR (%)^a</i>	<i>TTP (months)^a</i>	<i>MS (months)^a</i>
CMF		63	14	11.0	23.8
Anthracycline	291	67	14	10.2	20.2
No CT		68	22	12.5	27.5

^aAll differences were statistically not significant

RR: response rate; CR: complete remission; TTP: time to tumor progression; MS: median survival

or between the level of the MDR 1 protein (p-Gp), the response to CT, or the clinical outcome in metastatic breast cancer [31,32]. Nevertheless, some *in vitro* assays showed that the MDR 1-induced resistance affects the sensitivity of tumor cells for both anthracyclines and taxanes [33].

Could the subjective perception of the clinicians be involved in the actual trend towards excluding anthracyclines in favor of other drugs in advanced breast cancer?

Although response criteria of neoplastic diseases to anticancer drugs have been strictly codified to ensure objectivity, the possibility of the subjective implication of the clinicians in overestimating the efficacy of a new drug against an old one (the “wish bias”) has been described [34]. This aspect was particularly explored for anthracyclines (doxorubicin) and advanced breast cancer in a very interesting paper published by Fossati et al. [35]. They performed a retrospective analysis of 2234 patients enrolled in 29 studies during 1975-1999. A relative decrease of 11% in the odds of response to doxorubicin every 5 years was detected. In a multivariate analysis, including other factors related to the RR, this trend was statistically significant ($p=0.025$) and was compatible with the result of the test of the model adequacy (analysis based on residuals), suggesting the intervention of other confounders. Of note was the fact that, while complete response rate remained constant over time, the partial response mirrored the results for global response. Giving the fact that the interpretation of partial response involves more subjective judgment, the authors assumed the intervention of the “wish bias” in this difference, and recommended the use of double-blind methodology when assessing subjective end points.

What could we lose by excluding anthracyclines from the front-line treatment?

1. One of the best options for sequential or combination therapy in RBC, which has been proved to be useful for more than 20 years.

2. Some possible new perspectives which will remain unexplored in RBC. While taxanes are evaluated in order to find synergistic interactions (with trastuzumab, capecitabine, carboplatin, gemcitabine), the anthracyclines are left aside. For instance, the fact that the combination with trastuzumab leads to a high degree of cardiotoxicity does not mean that association with other promising targeted therapies may not be of value: the case of dual Her1 - Her2 complex inhibition with the tyrosin kinase inhibitor lapatinib [36,37].

3. The “best” treatment choice for some subcategories of patients. There is evidence pointing that Her2/neu amplification could represent a predictive marker for anthracycline sensitivity [38,39]. Despite the fact that trastuzumab is indicated in Her2/neu amplification (not recommended to be associated with anthracyclines due to cumulative cardiotoxicity), for some low-resource health systems trastuzumab is not available for large-scale use. Therefore, a potential “best” approach would be skipped. Moreover, several studies showed that, in some cases, breast cancer cells display a high topoisomerase II alpha level, and this amplification is correlated with a high sensitivity to anthracyclines [40-42]. For taxanes the data for this condition are controversial [42], some studies suggesting even a negative correlation [43]. On the other hand, other reports showed that taxanes could be particularly active in tumors with p53 mutations, while those with the wild type gene are more sensitive to anthracyclines [44,45].

What clinical consequences could emerge in the future following the rationale of “previous exposure” to a certain drug?

One of the “future” consequences has already occurred. We witnessed the FDA approval of a first-line option for RBC (paclitaxel/gemcitabine) following a phase III trial using a challenging comparator without anthracycline in any line [46]. The patients were considered “exposed”, after the use of anthracyclines in the adjuvant setting! Furthermore, there is a consistent trend for “pushing” the taxanes and the third generation aromatase inhibitors in the neoadjuvant setting [47-50]. Following the rationale of “previous exposure” what drugs should we use for the first-line treatment of relapsed breast cancer in those cases?

Is there any clinical evidence supporting the lack of interference between adjuvant anthracycline and the re-challenge with the same drug in relapsed breast cancer?

The answer is yes! During the 2005 ASCO meeting, the Japan Clinical Oncology Group presented a three-arm randomized phase III trial (JCOG 9802), evaluating the first-line chemotherapy for metastatic breast cancer [51]. They compared doxorubicin 40 mg/m² + cyclophosphamide 500 mg/m² (AC) with docetaxel (D) 60 mg/m² and an alternating regimen using AC-D. For the single-agent arms (AC and D),

the protocol allowed crossover to the other option if the disease was progressing during the first 6 cycles. Around 25% of the enrolled patients received adjuvant anthracyclines. There were no differences in terms of RR, time to tumor progression, time to treatment failure, or response duration, between the arms. Despite a significant overall survival advantage for D and AC-D versus AC (25.7, 25.0 versus 22.4, respectively), the subanalysis of patients receiving adjuvant anthracyclines showed no significant difference. Regarding this peculiar aspect the authors stated that “prior anthracycline use may not be a disadvantage in patients receiving first-line AC for MBC”.

Conclusion

Concluding this controversy, I believe that previous exposure in the adjuvant setting should not preclude the use of anthracyclines at relapse, according to the evidence available so far. However, I think this issue should be clarified in order to avoid confusion and bias while choosing first-line treatments in RBC. For some patients, with a particular clinicobiological tumor profile, anthracyclines could represent the most active agents, and replacing them following the “previous exposure” rationale, could spare this subcategory from a potential maximal benefit. Recent advances in molecular biology and translational research could provide essential information for more accurate evaluation of the predictive markers and tailoring the treatment accordingly. Establishing a standard first-line comparator for various clinicobiologic tumor profiles is mandatory for the design of future phase III randomized trials, exploring new first-line chemotherapy options in RBC.

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