BREAST CANCER
POSTANTHRACYCLINE THERAPY FOR METASTATIC DISEASE

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Standard chemotherapy of breast cancer: changing algorhitms for anthracyclines use?

KEYWORDS: Breast neoplasms; Anthracyclines; Cytotoxic drug therapy

INTRODUCTION

It has often been stated that metastatic breast cancer (MBC) is an incurable disease. However, this is not absolutely correct. With the exception of surgically curable individual cases, which are rather uncommon, the additional very small number of MBC patients treated with standard systemic therapy - may live very long. In fact, the long-lasting complete remission of the disease, as a surrogate of being potentially cured, is rare, but possible. Additionally, there are patients, whose diseases could be satisfactorily controlled by short-term or chronic systemic treatment, resulting in a long-lasting remission, or several successive remissions. Since the available methods do not allow to exactly discriminate the patients who achieved the transient complete remission, from those who are potentially cured, and those who are in "almost complete" remission, the expression "long-term survivors" seems appropriate for all of them. However, the vast majority of treated MBC patients will experience a new disease relapse, and die from their cancer. It was found that the median survival from the beginning of metastatic disease is improved from 11-12 months to 2-3 years in last decades. Therefore, the aims of MBC systemic treatment is still the best palliation with the lowest toxicity. This means the small prolongation of survival in the majority of patients and improved treatment options for those who relapsed regardless of good clinical remission. It also means increasing the proportion of long-living patients, either by improving the objective response rate, or by prolongation of any therapeutic response. These goals can be achieved by various approaches: The development of more active and less toxic drugs; the development of best chemotherapy combinations; the improved use of the biomarkers that predict chemotherapy sensitivity or resistance, thereby improving patients' selection for a particular treatment; also, the development of most powerful supportive drugs and best palliative care; finally, the re-analyses and improvement of the algorithms for the use of standard chemotherapy. Since the substantial proportion of all breast cancer (BC) patients still die from metastatic BC, the improvement of metastatic disease outcome could potentially contribute to the overall decline in BC morality, noticed in the last decade (1).

This paper presents the role of standard anthracycline chemotherapy in changing algorithms for MBC treatment.

STANDARD SYSTEMIC CHEMOTHERAPY OF METASTATIC BREAST CANCER

The development of current standard chemotherapy for advanced BC passed through several phases, including so-called pre-anthracyline and anthracycline periods. Mono- and poly-chemotherapy with non-anthracycline regimens significantly changed the MBC outcome and prolonged survival, compared to untreated disease. However the long-term survival remained rather exceptional (2). The introduction of anthracylines added significant gain in response rate, particularly in complete response, and duration of median time to progression. However, the overall survival prolongation was significant in relation to many mono- and combined chemotherapy regimens, but only marginally when compared to CMFp regimen (3). Although the new era with taxanes already began, promising to change the clinical course and the outcome of the disease, the importance of anthracyclines is not diminished: rather, the need for optimization of their use is recognized. Also, it became important to define for whom, and in which sequence, the non-anthracycline regimens, such as CMF-based ones, could be a better choice.

ANTHRACYCLINES IN THE TREATMENT OF METASTATIC BREAST CANCER

Hence, anthracyclines are still the most active standard treatment for MBC: median survival of MBC treated with standard chemotherapy is about 2-3 years. Median response rate with standard doxorubicin dose of 60-75 mg/m2 is 25-33% in patients previously treated with alkylating agents, being higher in chemotherapy-naive patients. Median time to progression was up to 4.5 months. Other anthracyclines did not add to a substantial benefit of doxorubicin. However, there are many controversies and limitations in their optimal use. Toxicity (among which cardiotoxicity is the most important) limits the use of anthracyclines: the total cumulative dose is cardiac risk-limited, the individual doses are hematology-toxicity limited, and any use is limited by the comorbid cardiac causes. Studies of how to overcome the cardiotoxicity and to allow the doses beyond maximal cumulative ones are extremely important for all responding patients (4).

The primary and especially acquired anthracycline resistance limits the use of other standard chemotherapeutics, in patients failing anthracyclines, requiring the development and use of new non-cross resistant drugs. However, a question arose of how to recognize the anthracycline-resistant disease in clinical practice. The multi-drug resistance, induced by anthracyclines, does not seem to be a stable genetic change. This suggests the definition of unequivocally resistant patients as those who relapsed while on anthracyclines (either with the failure as the best response, or after the initial response to anthracycline) (5). The anthracycline sensitivity, or resistance, could be unknown in patients who relapsed after achieving objective response followed by a progression-free interval. The same (6) or theoretically cross-resistant chemotherapy (5) could successfully been used.

ANTHRACYCLINES IN ADJUVANT CHEMOTHERAPY

Although the main goal of adjuvant therapy is to cure, the maximum benefit for the majority of early BC patients still concerns a significant delay of the first relapse and prolongs survival. Due to the substantial efficacy in MBC, anthracyclines were introduced into the adjuvant treatment. Later, it was confirmed that anthracyclines add a small, but significant benefit to non-anthracycline adjuvant chemotherapy (7). However, there still exists a substantial concern of the potential, and especially late cardiotoxicity, which might be underestimated. The need for correct evaluation of the role of adjuvant anthracyclines was recognized. Many studies have been conducted during almost 20 years, to find out the best regimen, optimal doses, and best sequence with other adjuvant therapies. Finally, it was necessary to define the patients who

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must not, and those who need not receive adjuvant anthracyclines, or to whom it should be recommended the CMF. This year the Consensus statement from St. Gallen supports strongly the anthracycline regimens as the best choice, retaining the recommendation of CMF for cases with cardiac contraindications, or for low risk subgroups (8.). Defining the best anthracycline regimen, the concern was expressed that ACx4 was a sub-optimal adjuvant treatment, at least for high-risk patients. Based on several studies, it seems that not only the dose, but also the duration of chemotherapy is important. Therefore, the standard should be FAC/FEC/CAF regimens (9). Concerning the high-dose adjuvant chemotherapy, it was concluded that standard doses were superior to less-than-standard doses, however the dose-intensity above the standard failed to show, until now, the benefit in adjuvant settings (10).

Obviously increasing use of anthracyclines in adjuvant settings induced many changes in the algorithms for recurrent disease. It arose again the question of the unknown resistance/sensitivity: there exists a chance, at least for some patients, to be deprived from the benefit of anthracycline re-treatment. The question is how to predict the sensitivity to anthracycline in anthracycline-pre-treated patients. At present, evidences from clinical studies suggest that doxorubicin given in the adjuvant therapy, does not ultimately cause the permanent multi-drug resistance (5). A time interval till the recurrent disease seems to be the only surrogate test of drug-sensibility.

BIOLOGICAL PREDICTION OF RESPONSE TO ANTHRACYCLINES

The possibility of chemotherapy response prediction by biological markers was examined since the discovery of steroid receptors, known predictors of response to endocrine therapy. Although it was expected that (negative) steroid receptors could predict the response to chemotherapy, this has never been confirmed. The well-known inverse expression of steroid receptors and growth factor receptors suggested the role of growth factor receptors as indicators of aggressive tumor growth, which could predict the response to aggressive treatments. Since the publication of results from GALGB study 8541, showing the better response to CAF chemotherapy in c-erbB-2 positive tumors, the extensive research was undertaken to confirm the intrinsic predictive role of c-erbB-2 (11). Until now, the non-equivocal evidences to recommend this biological marker for routine use was not obtained. Anyhow, this is one of the most exciting areas of biological research, in particular in terms of individualized adjuvant treatment selection.

ANTHRACYCLINES AND ENDOCRINE SENSITIVITY

It was found that tumors, containing both steroid receptors and c-erbB-2 might respond to tamoxifen. On the contrary, the chemotherapy commonly decreased the tumor SR content, and thus probably influenced the further response to endocrine treatments. Moreover, a detrimental effect of chemotherapy was found in SR+ patients in one study. Thus it appeared that sequential introduction of endocrine therapy and chemotherapy has remained optimal, at least for receptor positive MBC patients. Consequently, it is extremely important to make the careful patients' selection for which the anthracycline-based regimens, as a front-line systemic treatment, are the best choice.

CONCLUSION

The anthracyclines are currently recommended, either as the first- or second-line therapy for endocrine-resistant, clinically aggressive MBC, as well as for adjuvant treatment of high-risk early breast cancer, the almost only condition being the absence of cardiac risk.

The development of new potent anticancer drugs and biological agents effective in breast cancer, which interfere with the anthracycline activity and toxicity profile, required the intensive clinical investigations to find out the best way of their incorporation in standard treatment of MBC. Their optimal sequence, or concomitant use with anthracyclines, is expected to be defined soon. In addition, many clinical studies are on going to confirm the value of taxanes and biological agents in adjuvant settings. Therefore, the algorithms for breast cancer chemotherapy may be changed in near future towards novel and different order of chemotherapy regimens and combinations.

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Overcoming the problem of cumulative cardiotoxic dose in anthracycline - responding breast cancer patients

KEYWORDS: Breast cancer; Anthracyclines; Toxicity; Razoxane

1. ANTHRACYCLINES FOR BREAST CANCER

Anthracyclines are at the present pivotal drugs in the treatment of advanced or metastatic breast cancer and their use appears to be strongly advised in a subcategory of patients in adjuvant setting. Doxorubicin and Epirubicin are the two anthracyclines which achieved a worldwide approval for this indication, doxorubicin being more often present in consensus statements.

2. ANTHRACYCLINES CUMULATIVE DOSAGE

The principal problem with these two drugs is their toxicity profile, mainly their cardiotoxic potential. Both drugs cause cardiac myocyte damage which is not reversible and which can ultimately lead to drug-refractory congestive heart failure (CHF). For both drugs the concept of a total cumulative dose (TCD) has been evolved, over which the incidence of early or late CHF becomes inadmissibly high. The TCD for doxorubicin has been fixed at 500 mg/m^2, lower for patients with prior radiotherapy involving cardiac area, possibly lower for patients receiving concurrently cyclophosphamide. For epirubicin, the TCD is less well defined and situated in the range between 900 mg/m^2 and 1400 mg/m^2; it should be noted that epirubicin dosage per cycle is higher than doxorubicin dosage when the endpoint is similar antitumor activity on the same tumor type.

3. ANTHRACYCLINE- RELATED CARDIAC DAMAGE

Anthracycline related cardiac damage is mainly mediated by the intracellular $Fe^{++} \leftrightarrow Fe^{+++}$ cycling and facilitated by the paucity of antioxydant molecules in cardiac myocytes. Morphologically, the damage is characterized by different degrees of myocyte necrosis with no elements of inflammation, with consecutive fibrosis and impairment of retractile activity of the myocardium. The damage starts with doxorubicin at TCD of circa 200 mg/m^2, possibly earlier. Three grades of histological damage have been defined by Billingham (1); they correlate although not invariably with values of left ventricular ejection fraction (LVEF) which can be used for monitoring cardiac function during anthracycline treatment (2).

4. STOPPING ANTHRACYCLINE TREATMENT IN BREAST CANCER PATIENTS

There are two categories of breast cancer patients in whom anthracycline administration has to be stopped.

One of them is the category primarly refractory to anthracyclines or the category of patients in whom anthracycline resistance develops following initial response or stabilization. These patients deserve consideration of postanthracycline salvage chemotherapy modalities.

The other category comprises those patients whose response to anthracyclines is sustained, who would undoubtfully benefit from further anthracycline administration but in whom the treatment has to be stopped and other modalities considered because the cumulative dose has been reached. The question is whether there are any modalities that would permit further anthracycline administration without danger of CHF. We thus come to the concept of use of the so-called cardioprotectants.

5. CARDIOPROTECTION OR NOT WITH AMIFOSTINE

Data concerning cytoprotective agents for anthracyclines and their cardiotoxic effects emanate both from preclinical studies (3) and clinical trials (4). Amifostine has been extensively studied as a radioprotector and on several occasions there has been an interest in its activity as a chemoprocetor. The drug is at present commercially available, but its protective activity against anthracycline cardiotoxicity is still debatable. Data emanate mainly from in vitro models, i.e. either on perfused isolated rat heart (5) or on cultured neonatal rat heart myocytes (6). In these in vitro models, amifostine achieved cardiac myocyte protection when administered before anthracyclines. Since clinical data are still either insecure or lacking its clinical use as a cardioprotector is at present not reccomended.

6. CARDIOPROTECTION WITH DEXRAZOXANE (CARDIOXANE, ICRF-187)

Dexrazoxane is a bidioxipiperazine compound, which is an inactive molecule while in circulation. After entering the cardiac myocyte it is converted to a potent chelator, depleting intracellular iron and thus preventing the formation of the anthracycline-iron complex and iron redox cycling which is responsible for membrane lipid peroxydation and cardiac myocyte damage. Clinical studies have demonstrated that for adequate cardioprotection the dexrazoxane: anthracycline ratio should be 20:1 for doxorubicin and 10:1 for epirubicin. The drug should be applied about 30 minutes prior anthracycline administration.

7. CLINICAL STUDIES OF CARDIOPROTECTION WITH DEXRAZOXANE IN BREAST CANCER

On the model of FAC regimen in metastatic breast cancer, Kolarić and al. (7) have demonstrated that more than 50% of the patients when given dexrazoxane could receive doxorubicin at dose range 450-900 mg/m^2 without clinical or laboratory signs of cardiotoxicity;dexrazoxane was started with the first FAC cycle. On the same model, starting dexrazoxane with the first FAC cycle but in patients with preexisting heart damage or cardiac risk factors, Jelić and al. (8), using both MUGA-scan and echocardiography have demonstrated that no cardiotoxicity could be detected up to a cumulative doxorubicin dose between 800 and 1000 mg/m^2; however a LVEF decrease trend was noted with high total dosages, not exceeding 15% of the initial LVEF levels. Vici and al. (9) have demonstrated that dexrazoxane significantly protects against developpement of high dose epirubicin cardiotoxicity without adverse impact on antitumor activity.

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8. DELAYED ADMINISTRATION OF DEXRAZOXANE

Dexrazoxane administration increases the cost of anthracycline based treatment for advanced breast cancer. On the other hand, all breast cancer patients receiving FAC or similar regimens are not expected to be responders and in a significant percentage of them anthracycline treatment will be stopped because of primary or secondary resistance before cumulative dose has been reached. The question has arisen whether dexrazoxane could be, with the same efficacy administered in patients following demonstration that they were responders, i.e. after application of a dose of 200-300 mg/m^2 without cardioprotection. The answer was obtained by the study of Swain and al. (10) who applied dexrazoxane only after a cumulative doxorubicin dose of 300 mg/m^2 has been reached. Dexrazoxane proved to be a highly effective cardioprotective agent when used in patients with advanced breast cancer who continue to receive doxorubicin based chemotherapy after a cumulative doxorubicin dose of 300 mg/m^2 has been reached.

CONCLUSION

In conclusion, for the moment dexrazoxane remains the only available cardioprotective drug permitting overcoming of doxorubicin-related cardiotoxicity hazards in patients who would benefit from further anthracycline treatment once the cumulative dose has been reached;the conclusions could be summarized as follows: dexrazoxane permits cardiotoxic doses of doxorubicin to be given without cardiotoxicity;patients with cardiac risks factors can be treated with full doses of doxorubicin when given dexrazoxane; dexrazoxane permits second-line treatment with other cardiotoxic drugs (11); even when using dexrazoxane, serial determination of LVEF once the cumulative anthracycline dosage has been reached is a must (8).

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Breast cancer: what after anthracyclines?

KEYWORDS: Breast cancer; Anthracyclines; Drug resistance; Salvage therapy

Metastatic breast cancer (MBC) is moderately chemotherapy-sensitive neoplasm. Despite a large number of active agents (more than 40), that exist for its treatment, MBC is essentially incurable disease with currently available therapy. For almost thirty years, anthracycline-containing regiments (ACR), are considered as the most effective combination, and represent the treatment of choice for metastatic breast cancer producing an overall response rate of 50-80%, median response duration of 8-15 months and median survival of 17-25 months (1). ACR are or become ineffective in at least one of five women treated for metastatic breast cancer. These patients are subsequently found to have anthracycline resistance (intrinsic or acquired) which is fundamental reason for clinical failure. On the other hand, with the increasing use of anthracyclines in adjuvant setting, we are faced with the problem of postanthracycline chemotherapy in patients with disease relapse. Irrespectively whether ACR was applied, in adjuvant or metastatic setting, there are two groups of patients: a) anthracycline resistant patients and b) patients who experienced progressive disease after previous response to anthracycline without development of drug resistance.

Resistance of human breast carcinoma to anthrracycline is mediated by different drug resistance mechanisms including multidrug resistance (MDR), modification of topoizomerase II activity, reduction of fluidity of cell membrane or increase of effectiveness of DNA repair mechanisms (2). Unfortunately, biochemical drug resistance does not ultimately translate into a clinical one. While drug resistance in preclinical studies can be defined in terms of the cytotoxic effects of defined drug concentration, clinical definition are based not only on the tumor response (3) but also on the time to treatment failure (4). The most stringent definition of clinical anthracycline resistance (3) was reported as progressive disease during ACR with no intervening response or as relapse during adjuvant chemotherapy (primary resistance). Secondary resistance was defined as initial response during ACR followed by progressive disease. Relapse that occur within 6 or 12 months of the last dose of anthracycline therapy is not marker of anthracycline resistance, but rather may indicate accelerated regrowth after effective chemotherapy (3). Furthermore, these criteria were extended by some authors (5). Relapse within 12 months from adjuvant therapy was classified as secondary resistance, while disease progression more than 30 days after chemotherapy

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was classified as not anthracycline resistant disease.

Patient experiencing progression after previous response to ACR for advanced disease, without development anthracycline resistance, represents another group with different clinical features. In this group, complete clinical response (CR) to first line chemotherapy (e.g.FAC), range between 15-20% (6). According to Puztai et al (7), it appears that there is significant correlation between duration of CR and overall survival. This suggest that chemotherapy when induces CR may prolong survival. Resistance of human breast cancer to anthracycline is negative prognostic factor, and predicts a reduction in the efficacy for the most other cytotoxic drugs. The objective response rate to second-line chemotherapy with conventional drug (mitoxantrone, metotrexat, vinblastine, vindesine, mitomycin, cisplatin, melphalan) is achieved in 5% to 7.7% of these patients, with median survival of 5 months (3).

At the Institute of Oncology and Radiology of Serbia in 1995, an open non-randomized phase II study was initiated (8) to assess the activity and toxicity of mitoxantrone-5 fluorouracil-low dose leucovorin as second-line chemotherapy in metastatic breast cancer patients resistant to doxorubicin (PD after II cycles of FAC chemotherapy or SD after IV cycles of FAC chemotherapy). A total of 22 patients entered the study, and 19 of them were assessable for response. There was no complete remission (CR=0), partial remission was achieved in 5% of patients (median duration 15 months), stabilization was observed in 37% of patients (median duration 11 months), and 58% of patients experienced progressive disease. Median survival for the whole group was 8 months (range 0-24). Although prolonged disease stabilization was noticed in some patients, from the strict objective-response point of view, mitoxantrone+5-fluorouracil+low-dose leucovorin, is in-effective regimen for the treatment of anthracycline resistant advanced breast cancer.

Until the last few years, mitomycin C plus vinblastine was the most frequently used combination after first line anthracycline-containing regiments in the treatment of MBC (RR vary from 7% to 40%, and median survival is usually between 6-9 months)(9,10). A literature review did not identify strong arguments in favor of any conventional chemotherapy regimen in this setting.

In the 1990s, the paradigm of using established combination chemotherapy is shifting to the dose-dense strategy of sequentially administering new single agents (11), which offer attractive therapeutic options. While some of these drugs induce response rates at least equivalent to those achieved by older one, the other have improved safety profiles, or are easier to administer. Among the new agents isolated in recent years, the taxanes (paclitaxel et docetaxel) seem to be most promising in postanthracycline therapy. Phase II studies revealed response rate of 26-47% for paclitaxel and 57-66% for docetaxel given as second-line monochemotherapy (12). Docetaxel produces an overall response rate up to 41% in anthracycline resistant breast cancer (13,14). In randomized phase III of docetaxel versus mitomycin-vinblastine (MV) in MBC progressing despite previous ACR (5), docetaxel produced a higher response rates than MV (30% vs. 11,6%), even in anthracycline resistant patients (29,6% vs. 6,7%). In clinical practice, the taxanes (alone or in combination with other anti-neoplastic drugs) are becoming the new standard chemotherapy approach for patients with MBC progressing despite previous anthracycline-containing chemotherapy. Vinorelbine is another new active agent in breast cancer, with RR about 20% in salvage treatment (15). In anthracycline resistant patients, vinorelbine achieved RR in only 16% of patients, although it was superior (phase II) in comparation with melphalan (16% vs. 9%) (16). Vinorelbine plus cisplatin combination produced RR in 49% of patients previously treated with anthracyclines, and more importantly RR in 44% of patients with anthracycline refractory MBC (17). Capecitabine is the first oral fluoropyrimidin for the treatment of patients with MBC who failed prior doxorubicin chemotherapy. Randomized phase II (18), showed better efficacy of capecitabine vs. paclitaxel in patients failed previous anthracycline chemotherapy (36% vs. 26%). Many other agents such as oral etoposid (19), platinum compounds, continuous-infusion of fluorouracil and newer oral surrogates (tegafur), gemcitabine, raltitrexed, edatrexate and losoxantrone are under intensive study in several trials. In addition to these chemotherapeutics, trastuzumab (Herceptin), a novel monoclonal antibody directed against the protein product of the HER 2 oncogene, produced a response rate of approximately 16%(20) in a cohort (HER 2 positive MBC) in which 68% of patients had been treated and had failed anthracyclines and paclitaxel. More importantly, trastuzumab (T) in combination with cytotoxic drugs caused the improvement of therapeutic activity over the chemotherapy alone (21). In the case of previous anthracycline exposure, the current best option appears to be the combination of trastuzumab with paclitaxel. Other trastuzumab-chemotherapy combination (T+vinorelbin, T+platinum agents+docetaxel) may also prove valuable and the results of ongoing clinical trials are eagerly awaited (22).

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The role of the taxanes in postanthracycline treatment of metastatic breast cancer patients

KEYWORDS: Breast neoplasms; Salvage therapy; Docetaxel; Paclitaxel

According to the results showing better response rate with anthracycline polychemotherapy versus non-anthracycline regimens, anthracycline-containing combinations may still be considered as standard first-line therapeutic option in metastatic breast cancer patients. On the contrary, until recently there was no consensus on the choice of chemotherapy in advanced breast cancer after anthracycline-based regimens have failed.

The introduction of the taxanes in the last decade has been the most encouraging chemotherapy achievement after a 15-year period of little progress in the development of new drugs for breast cancer. The taxanes have emerged as the most powerful compounds and the results available to date suggest slightly increased activity of docetaxel compared to doxorubicin, at least in terms of RR (1). Moreover, combinations of taxanes and anthracyclines have shown higher efficacy of the combination over standard anthracycline-based regimens: paclitaxel-doxorubicin vs FAC-better RR, TTP and overall survival (2). Today the data are compelling that for patients who have received prior anthracycline-based therapy taxanes are the next treatment of choice. This conclusion is based on the following facts: 1) the general inferiority of previously used agents or regimens, in terms of response rate and toxicity; 2) the relative (although not complete) lack of cross-resistance between taxanes and anthracyclines; 3) the acceptable toxicity of these agents in previously treated patients; and 4) emerging data indicating that the use of taxanes in a salvage setting provides superior response rates and overall survival compared with previously used salvage regimens (3,4).

The two taxanes share some characteristics, but are also significantly different both in preclinical profile and, most importantly, in clinical characteristics. The main clinical differences are related to their different efficacy-toxicity ratio in relation to dose and schedule. Both agents bind reversibly to the beta subunit of tubulin and induce tubulin polymerization. Normal microtubules need to maintain a balance between polymerization and depolymerization. The taxanes disrupt this balance, leading to arrest at the G2/M phase of the cell cycle.

From the variety of early studies performed with paclitaxel (Taxol®) using several infusion schedules, neutropenia appeared to be the main toxicity, being more profound for longer infusional schedule and higher doses;other adverse events related to the drug included neurotoxicity, mucositis and vomiting, alopecia, myalgia and arthralgia, fatigue, skin reactions and hypersensitivity reactions which led to use of steroid premedication. With respect to docetaxel (Taxotere®), the dose limiting toxicities were mostly related to neutropenia, mucositis and hypersensitivity. Concerning the term "toxicity" in a broad sense it seems that paclitaxel produces more neurotoxicity, and docetaxel induces somewhat more neutropenia and significantly greater fluid retention. In addition, paclitaxel may be tolerable for a longer period than docetaxel (5).

In patients with anthracycline-resistant metastatic breast cancer, paclitaxel produced RR of 6% to 48%. Several different doses and schedules of paclitaxel have been investigated and the optimal administration regimen has yet to be determined. The recommended doses for single-agent paclitaxel are 135 mg/m^2 to 175 mg/m^2 given over 3 hours every 3 weeks (6,7).

Docetaxel has been recommended for breast cancer at doses ranging from 60-100 mg/m^2 administered as a 1-hour infusion every 3 weeks. Docetaxel is highly effective agent in patients with anthracycline-resistant breast cancer producing RR of 32% to 57%(6,7). In two studies published simultaneously, the objective RR to docetaxel in patients with breast cancer resistant to anthracyclines were 53% and 57%, respectively. This excellent RR was confirmed in randomized trials. In the largest study (392 patients), docetaxel 100 mg/m^2 over 1 hour was compared to mitomycin C plus vinblastine in patients with anthracycline-resistant metastatic breast cancer. Patients treated with docetaxel had significantly better RR (30% vs. 11,6%), TTP (19 vs. 11 weeks) and overall survival (11.4 vs. 8.7 months) (8). Another study (283 patients) compared docetaxel (100 mg/m^2 over 1 hour) with sequential methotrexate and 5-FU administered to patients with advanced anthracycline-resistant breast cancer. Preliminary results from this phase III trial indicate that docetaxel appears to be more active than the sequential combination of methotrexate and 5-FU. RR (42% vs. 19%) and median TTP (6 vs. 3 months) were significantly better in the docetaxel arm, again demonstrating that docetaxel is effective therapy against anthracycline-resistant breast cancer (9).

The only randomized trial comparing docetaxel (100 mg/m^2 - 1 h infusion) and paclitaxel (175 mg/m^2 - 3 h infusion) in patients with previous exposure to anthracyclines is nearing completion. Data should be available in 2002 and will further clarify the situation of relative efficacy-toxicity ratio of these agents.

The interesting study was conducted to evaluate the efficacy of docetaxel 60 mg/m^2 in 3-weekly schedule according to the strictly defined status of anthracycline resistance in metastatic breast cancer patients. The results showed that docetaxel was effective in metastatic breast cancer with secondary resistance to anthracycline and stressed that status of anthracycline resistance is important for the prediction of response to second-line treatment with docetaxel (10).

The taxanes can be safely administered on weekly schedule with preserved efficacy. However, administration of taxanes on a weekly schedule significantly changes their toxicity profile. Both agents cause mild myelosuppression and less hypersensitivity reactions compared to 3-weekly schedules. The dose-limiting toxicity for weekly paclitaxel is peripheral neutropathy and the optimal starting dose is 80 mg/m^2/week. For weekly docetaxel, the optimal dose is 35-40 mg/m^2/week, and the most common limiting toxicities are neutropenia and fatigue (11).

As taxanes are shown to be the most active agents used as monotherapy in post- anthracycline setting, the issue of special interest is whether the combination of taxane with other antineoplastic agents would be superior to taxane alone. In anthracycline-resistant metastatic breast cancer various drugs have been investigated in combination with a taxane, such as cisplatinum, capecitabine, vinorelbine, gemcitabine, herceptin.

Most recently, data from a large (511 patients), randomized, phase III trial have shown that the addition of capecitabine to docetaxel in anthracycline-pretreated patients results in significantly superior RR, TTP, as well as overall survival compared with docetaxel monotherapy (12). FDA has approved this

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new therapy combination for the treatment of patients with metastatic breast cancer in whom prior anthracycline chemotherapy has failed.

At the Institute for Oncology and Radiology of Serbia a study with docetaxel-mitomycin-vinblastine combination chemotherapy was performed aimed to investigate the safety and efficacy of this combination in patients with clinical resistance to anthracycline-based chemotherapy. The results obtained among 37 patients showed high activity of the combination (exciting RR 40%) with acceptable safety profile in anthracycline-resistant metastatic breast cancer patients (13).

In summary, both taxanes are excellent choices for the second-line treatment of patients with metastatic breast cancer previously exposed to anthracyclines and presently the taxanes may be considered as standard therapeutic option for anthracycline resistant metastatic breast cancer patients.

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New therapeutic option in breast cancer: trastuzumab (Herceptin®) in combination with chemotherapy

KEYWORDS: Breast cancer; Trastuzumab; Growth factor receptors

During last two decades, new prognostic and predictive markers have been identified in order to provide more efficacious treatment and to prolong survival of breast cancer patients. The most thoroughly investigated is a group of growth factors, their receptors and cascade signaling molecules such as four-member human epidermal growth factor (HER) receptors family, among which EGFR and HER-2 are the most important.

HERs bind their growth factors as dimers and transmit cellular signals. Although HER-2 specific ligand has not yet been recognized, HER-2 is a preferred heterodimeric partner, and HER-2 containing heterodimers are long-lived and their signals are relatively potent (1). HER-2 protein is encoded by HER-2 or c-erbB-2 gene located on the chromosome 17 and its amplification ultimately results in HER-2 protein overexpression. HER-2 overexpression is present in up to 30% of patients with invasive breast cancer, and serves as poor prognostic marker. According to mostly retrospective analyses of HER-2 status on tumor material derived from breast cancer patients included in prospective studies, HER-2 overexpression appears to be a marker of anthracycline sensitivity, and CMF and tamoxifen resistance (2).

However, prospective clinical studies confirmed that HER-2 expression could be used only to select breast cancer patients who are suitable for immunotherapy with trastuzumab (Herceptin®). Trastuzumab is a recombinant human anti-HER-2 monoclonal antibody, which causes marked down-modulation of HER-2 through the enhancement of receptor endocytosis and degradation, and the inhibition of heterodimeric formation, especially HER2/HER3 and HER2/HER4 heterodimers. In some breast cancer cell lines it also induces the cell cycle arrest in G0/G1 phase. Furthermore, trastuzumab stimulate the immune response through antibody-dependent cell cytotoxicity (ADCC) process (3).

Phase I clinical studies showed that trastuzumab was well tolerated with intra-venous weekly administration. Fever and chills grade 1/2 were the most

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frequent adverse events related to the drug. The results of pivotal phase II clinical study conducted on 222 heavily pretreated HER-2 positive advanced breast cancer patients showed modest activity of trastuzumab, with response rate not exceeding 15% (4). High incidence of significant cardiotoxicity expressed either by the significant fall of heart ejection fraction, or clinically overt cardiac insufficiency, was noticed in up to 7% of these women. However, all of them had either underlying heart disease, or were previously treated with maximal cumulative dose of anthracyclines.

Further clinical research of trastuzumab in breast cancer confirmed much higher efficacy of trastuzumab in combination with cytotoxic drugs. Slamon et al conducted randomized open-label phase III clinical study to compare the efficacy and tolerability of first-line combination of trastuzumab and chemotherapy with chemotherapy alone. The patients with HER-2 positive metastatic breast cancer not previously treated with chemotherapy for advance disease, were randomized in two treatment arms: chemotherapy alone (combined doxorubicine and cyclophosphamide or paclitaxel) or the combination of trastuzumab and chemotherapy. The objective response rate was significantly higher (30% vs. 32%, $p< 0.01$), and time to disease progression (7.4 vs. 4.6 months, $p<0.001$) and overall survival (25 vs. 20 months, $p<0.05$) were significantly longer in the trastuzumab group. Unfortunately, a significantly higher rate of serious cardiotoxic events (up to 27%) occurred in the anthracycline-trastuzumab group, which prevents the recommendation of this combination for routine practice.

Our single center experience with 11 metastatic HER-2 positive breast cancer patients treated with the combination of trastuzumab and paclitaxel confirmed favorable tolerability of this regimen, grade 1/2 fever and chills being the most frequent non-hematological toxic effects. As far as cardiotoxicity is concern we noticed neither significant fall of the ejection fraction determined with US exam or MUGA scan, nor symptomatic heart insufficiency (Figure 1).

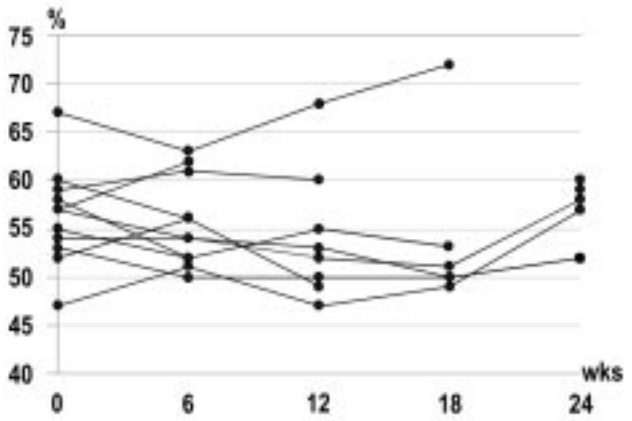

Figure 1. Ejection fractions of patients during combined treatment with trastuzumab and paclitaxel

Recently reported studies of the combination of trastuzumab with chemotherapy showed high efficacy of this therapy in heavily pretreated metastatic breast cancer patients with HER-2 overexpression (Table 1).

Table 1. Efficacy of the combination of trastuzumab (Herceptin®) and chemotherapy

author	phase	N	regimen	RR(%)
Burstein et al (6)	II	40	Navelbine+H	75
Seidman et al (7)	II	95	Weekly paclitaxel +H	57* 67-81**
Gianni L et al (8)	II	16	Doxorubicin+paclitaxel +H	14/16
Theodoulou M et al (9)	II	20	TLC D-99+H	60
Slamon D et al (10)	II	62	Docetaxel+CBDCA +H	84

RR: response rate; H: Herceptin; CBDCA: carboplatine; TLC D-99: Liposome-encapsulated formulation of doxorubicine
* according to intent to treat analysis; ** in HER-2 overexpressors, dependent on type of HER-2 analysis

The significant cardiotoxicity was not reported in these studies including the combination of trastuzumab with doxorubicine and paclitaxel (8). The mechanism of trastuzumab mediated enhancement of doxorubicine-related cardiac damage has not yet been resolved. The interaction of trastuzumab with HER-2 overexpressing myocardium is not likely to be the point. Another important issue addressing HER-2 overexpression and response to Herceptin emerged from these studies. Precisely, it seems that the best predictor of response to trastuzumab is gene amplification measured by fluorescent in situ hybridization (FISH+) and HER-2 protein overexpression measured by immuno-histo-chemistry (IHC) at 3+ level.

Trastuzumab was the first signal transduction modifier which translate one promising area in laboratory research into the routine practice in medical oncology. More importantly, trastuzumab for the first time clinically proved that the manipulation of growth factor signaling could enhance sensitivity to cytotoxic drugs, which is really a step forward to the individualization of anti-tumor therapy.

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Salvage chemotherapy for metastatic breast cancer: what are the current options after failure to both anthracyclines and taxanes ?

KEYWORDS: Breast cancer; Neoplasm, metastases; Salvage therapy; Capecitabine

The trend towards more aggressive treatment earlier in the disease course with agents such as anthracyclines and, particularly, taxanes, and the use of highly active agents in the adjuvant setting, have led to an increase in the number of patients presenting with metastatic disease that is resistant to or had failed both anthracyclines and taxanes. Patients who have been heavily pretreated for metastatic disease present a particular problem as they are often symptomatic and have very few treatment options. Further chemotherapy is of limited benefit because toxicity and diminished quality of life often outweigh gains from tumor regression. On the other hand, at least a quarter of patients previously treated with two or more chemotherapy lines for metastatic disease, despite their progressive disease, stay still in a good general condition. For those patients, who could be successfully treated in terms of good palliation and even prolonged survival, there are still no standard therapeutic approaches and new strategies are needed.

The ideal cytotoxic agent in palliative setting offers a reasonable prospect of antitumor response leading to a reduction in tumor-related symptoms with improved quality of life and minimal toxicity. In pretreated metastatic cancer patients only few agents or their combinations, such as oral etoposide and cisplatin or carboplatin plus etoposide, have revealed some effect in these patients (1). Among new chemotherapy agents used in salvage treatment for patients with metastatic breast cancer that have progressed following anthracycline and taxane therapy, capecitabine was the most thoroughly investigated drug (2).

Capecitabine (Xeloda) was rationally designed as an orally administered, tumor - selective, fluoropyrimidine derivate whose activity clinically mimics continuous infusional 5FU. Capecitabine is a prodrug that is converted by a series of three enzymatic reactions to 5FU. The final enzymatic step is catalyzed by thymidine phosphorylase (TP), which is overexpressed in a number of human cancers (breast, cervical, colorectal and stomach), allowing capecitabine to be finally converted to 5FU at the tumor site. This tumor-selectivity potentially improves efficacy and safety by enhancing tumor drug concentrations and hence minimizing systemic exposure to 5FU (3).

Clinical trials have demonstrated that capecitabine is an effective treatment for metastatic breast cancer. Two large, multicenter, phase II studies including more than 230 patients have documented the activity of capecitabine in heavily pretreated patients who are refractory to or have failed treatment with anthracyclines and taxanes.

The first study of capecitabine in breast cancer involved 162 women previously treated with paclitaxel for metastatic disease (4). Of these, 37(23%) were classified as paclitaxel failures, and 124(77%) as paclitaxel-resistant. Of 147 (91%) patients who had also received previous anthracycline treatment, 42 were designated as having failed therapy, and 67 as being anthracycline resistant. Capecitabine was administered as 2510 mg/m2/day in two divided doses for 14 days, followed by 1 week rest, repeated every 3 weeks. In this heavily pretreated patient population, capecitabine resulted in response rate of 20%, with an impressive 29% response rate in subpopulation of patients refractory to both paclitaxel and doxorubicin. An additional 43% of patients achieved disease stabilization, leading to overall disease control in more than 60% of patients. The median duration of response was 8.1 months and the median overall survival was 12.6 months. According to these results FDA approved capecitabine for the treatment of metastatic breast cancer patients who failed both doxorubicin and paclitaxel therapy.

The findings of the pivotal trial have been confirmed in a second study involving 74 metastatic breast cancer patients that had progressed after anthracycline and taxane (paclitaxel or docetaxel), where capecitabine produced response rate of 25% (5).

Capecitabine is generally well tolerated, with a safety profile typical of infusional fluoropyrimidines. It is rarely associated with life-threatening adverse events and the most common toxicities were hand-foot syndrome, diarrhea and nausea. Alopecia and bone marrow suppression were rare with capecitabine treatment. Grade 4 clinical adverse events were infrequent (3.4%), and adverse events were manageable by treatment interruption and dose reduction, if necessary. A retrospective analysis of data from four clinical trials conducted in breast cancer patients indicated that in patients who began treatment at the recommended starting dose, dose reduction for adverse events did not have a negative impact on the efficacy of capecitabine (6).

Preclinical studies have demonstrated that sensitivity to capecitabine correlates with tumor concentrations of TP. The role of TP in the conversion of capecitabine to 5FU in tumor tissue offers the potential to further increase the efficacy of capecitabine through intratumoral TP upregulation. A number of cytotoxic agents, including taxanes, vinorelbine, cyclophosphamide, mitomycin C, herceptin, as well as tumor irradiation, are known to increase the activity of TP in tumor cells. This synergy observed between capecitabine and other agents was rationale for clinical trials aimed to investigate capecitabine combination therapy. In metastatic breast cancer patients previously exposed to anthracycline and taxane therapy, capecitabine plus vinorelbine combination was well tolerated, producing promising efficacy (7).

Clinical trials have established the efficacy and tolerability of capecitabine as treatment for anthracycline and taxane-pretreated metastatic breast cancer, providing an effective therapy option for patients who have exhausted all other active agents in this disease (8). Moreover, oral administration enables convenient, patient-oriented, home-based therapy, which most patients prefer to intravenous treatment administered in the clinic (9).

Vinorelbine (Navelbine) is another new generation active agent in breast cancer. Vinorelbine, novel vinca alkaloid, is a cell cycle-specific microtubule inhibitor. In contrast to the taxanes, vinorelbine destabilizes the microtubules. In vitro studies it showed a selective effect on non-neuronal microtubules, which may explain the decreased neurotoxicity of vinorelbine compared with other vinca alkaloids.

As a single agent, when delivered IV at 25-35 mg/m^2 on days 1 and 8 of 3 week cycle, vinorelbine is associated with less than 20% response rate in

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salvage setting (10). Given in a dose-intensive weekly schedule (35 mg/m^2/w) in combination with granulocyte-colony stimulating factor in patients pretreated with anthracycline and paclitaxel, vinorelbine increased a response rate up to 25% (11). Applied as a second or third-line chemotherapy vinorelbine and protracted infusional fluorouracil achieved promising results: a response rate of 61% and median survival of 22 months. The low incidence of alopecia and other nonhematologic toxicities makes vinorelbine particularly attractive as a safe agent for palliative treatment of metastatic breast cancer. Granulocytopenia, the dose-limiting toxicity of this agent, is transient, and rarely results in life-threatening events.

At the Institute for Oncology and Radiology of Serbia, there is an ongoing trial of salvage capecitabine-leucovorine-vinorelbine combination chemotherapy in both anthracycline and taxane-resistant metastatic breast cancer patients. The aim of the study was to assess the safety and activity of the combination. According to the preliminary results, this combination appears to be active with a good safety profile in the subpopulation of patients with the poorest prognosis.

Gemcitabine (Gemzar), a new agent with novel mechanism of action affecting pyrimidine synthesis and inhibition of ribonucleotide reductase, has demonstrated efficacy in a variety of solid tumors, including metastatic breast cancer. In the largest study evaluating the safety and efficacy of the drug, gemcitabine as a single agent (800 mg/m^2/week for 3 weeks of a 4-week cycle) produced the response rate of 25% in pretreated metastatic breast cancer patients (12). The median survival was 11.5 months. The main toxicity was hematological, although only 1 of 44 patients developed neutropenic sepsis. Other studies suggest that single-agent gemcitabine, as well as its combination with other agents such as cisplatin (13), is safe and effective and should be an option as salvage chemotherapy for patients who failed anthracycline and taxane therapy.

Presently, there is no established treatment for patients with metastatic breast cancer that have progressed following anthracycline and taxane therapy. Therefore, there is still an unmet medical need for effective and well-tolerated therapies for this patient population (14). So, the development of novel anticancer agents continues on several fronts. One approach is to develop analogues of older drugs with improved efficacy and/or safety profiles (e.g. new oral fluoropyrimidines). A second approach is to study agents that belong to classes of compounds that historically have had little activity against breast cancer cells (e.g. topoisomerase I inhibitors). A third strategy is to interfere with mechanisms of drug resistance using inhibitors of the multidrug resistance pump. There are over 300 new compounds in a phase of clinical development in oncology today, and a majority of them represent cytotoxic drugs. In addition to cytotoxic chemotherapy, there is a great interest in developing novel molecular-based therapeutics targeted at inhibition of tumor cell proliferation pathways. Promising targets include growth factor receptors and their ligands, intracellular signal transduction molecules, cell-cycle regulatory proteins, and transcription factors (15). The incorporation of these new biologic agents in conventional therapy, by improving treatment individualization, hopefully will contribute to the progress in management of metastatic breast cancer.

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