First line chemotherapy of metastatic breast cancer

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In the last 20–30 years the approach to metastatic breast cancer by chemotherapy has been largely studied. Anthracyclines, taxanes and, more recently, capecitabine and gemcitabine represent the breakthrough of treatment. In the next future the combination of chemotherapy and target therapy will be considered more frequently.

Key words: metastatic breast cancer, chemotherapy, trastuzumab

Breast cancer is the second most frequent cause of cancer death in women in the United States after lung cancer. Estimates indicate that 211,240 female breast cancer cases and 40,410 will occur in 2005.

Sixty-five percent newly diagnosed cases and 77% deaths are caused by this tumour [1, 2]. Despite advances in prevention, screening and therapy of breast cancer, about 50% of patients have a node-positive tumour at time of diagnosis, and 60% will develop a metastatic disease [3].

when to start with chemotherapy?

It is possible to maintain that, more or less late during their clinical history, almost all patients with advanced breast cancer receive chemotherapy.

The patients with metastatic breast cancer are a heterogeneous population; therefore, the goals of therapy range from symptom palliation and minimisation of toxicity in elderly women with indolent disease, to prolongation of overall survival in younger women, with good performance status, aggressive visceral disease and overexpression of Her-2.

In particular, cytotoxic chemotherapy with the most active drugs is generally the first treatment’s option for patients with hormone-receptors negative disease, or with hormone refractory tumour, and in whom impending organ failure require a rapid response.

The patients with metastatic breast cancer overexpressing the oncoprotein c-erb-B2 represent an interesting sub-population who deserves particular attention.

In daily practice, the choice of chemotherapy regimen depends on several factors concerning not only the tumour’s characteristics, but also the patient, so the clinician must consider the following: if the patient underwent prior chemotherapy (including previous adjuvant treatment); if she has a good performance status, or any co-morbidities, as well as the toxicity profiles; the organization of schedule, and the disease’s characteristics as relapse-free interval from adjuvant therapy, clinical aggressiveness, sites of metastasis. Finally, but no less important, the clinician also must to consider the patient’s preference.

which agents?

Usually, anthracyclines and taxanes are the most active and employed cytotoxic drugs for the treatment of metastatic breast cancer. These drugs, as single agents, yield an objective response in 20–80% of patients with metastatic disease [4–6].

The treatment with anthracyclines is associated with an increase in response rate, remission duration and survival of patients with metastatic disease, with approximately 20% of complete responders still disease free 10 years after achieving a complete response [7, 8].

It is generally recognized that polychemotherapy yields a higher response rate than single-agent chemotherapy, but its impact on overall survival is less well documented. Moreover, a Fossati’s meta-analysis and a systematic review of randomized trials evaluating different approaches of first line chemotherapy in metastatic breast cancer, showed that the death’s risk decreases with polychemotherapy than single agent therapy of 28%, with anthracycline-containing regimens than non anthracycline therapy of 4%, and of 10% with taxane-containing regimens [9–11] (Table 1).

Recently, paclitaxel and docetaxel, showed to be the most active drugs for metastatic breast cancer. The administration of a taxane as single agent yields a significant increase in overall survival, in particular for the patients with a metastatic breast cancer resistant or refractory to an anthracycline-containing regimen [12], also this therapeutic approach produces about 50% up to 68% of overall response rate in chemotherapy patients [13–21].

Moreover, recent studies demonstrated an advantage for combination over single-agent regimen, if we associate a new
drug, such as gemcitabine or capecitabine. In fact, in a phase III study in anthracycline pre-treated patients, O’Shaughnessy showed not only an increase of the objective response rate, but also a gain in time to progression and overall survival with the combination of docetaxel 75 mg/mq on day 1 plus capecitabine 1250 mg/mq on day 1–14 every 21 days versus docetaxel as single agent [22]. Similar results, with a statistically significant increase in objective response rate, time to progression and overall survival has obtained in a multicenter phase III trial by Albain et al., with the combination of the gemcitabine plus paclitaxel compared to paclitaxel as single agent [23], so paclitaxel 175 mg/mq on day 1 and gemcitabine 1250 mg/mq on days 1, 8 represents a new standard for the first line treatment of patients with advanced breast cancer (Table 2).

The toxicity profile is an important factor in determining optimal combination therapy: balancing of the efficacy and safety is a key goal for delivering a positive risk-benefit profile for each patient. Gemcitabine, capecitabine and docetaxel are highly active agents in anthracycline-pretreated metastatic breast cancer. A recent study compared gemcitabine plus docetaxel versus capecitabine plus docetaxel providing valuable information for a clinician in choosing an optimal treatment. This phase III trial showed that gemcitabine plus docetaxel is an active regimen in advanced breast cancer with similar efficacy to capecitabine plus docetaxel, but the toxicity profile favours gemcitabine plus docetaxel in terms of less grade 3 hand-foot syndrome (0 vs. 26%), less grade 3/4 diarrhea (7 vs. 18%), less grade 3/4 mucositis (4 vs. 17%), less drug-related discontinuations (13 vs. 28%). So gemcitabine plus docetaxel is a new treatment option for metastatic breast cancer patients [24].

**Table 1.** Meta-analysis of randomized trials

<table>
<thead>
<tr>
<th>Treatment arms</th>
<th>No. of patients</th>
<th>ORR (%)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly vs. single</td>
<td>2442</td>
<td>1.79*</td>
<td>0.82*</td>
</tr>
<tr>
<td>Antra vs. non-antra</td>
<td>5241</td>
<td>1.30*</td>
<td>0.96</td>
</tr>
<tr>
<td>Taxane vs. non-taxane</td>
<td>3643</td>
<td>1.29*</td>
<td>0.90*</td>
</tr>
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</table>

*Significant difference.


**Table 2.** Outcome for taxane regimens

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment arms</th>
<th>D</th>
<th>MTX+5FU</th>
<th>D</th>
<th>VLB+MMC</th>
<th>D+X</th>
<th>D</th>
<th>G+P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (months)</td>
<td>NS</td>
<td>42</td>
<td>21</td>
<td>30</td>
<td>12</td>
<td>42</td>
<td>30</td>
<td>39</td>
<td>39.3</td>
</tr>
<tr>
<td>OS (months)</td>
<td>11.4</td>
<td>8.7</td>
<td>14.5</td>
<td>11.5</td>
<td>15.8</td>
<td></td>
<td></td>
<td></td>
<td>15.8</td>
</tr>
<tr>
<td>TTP (months)</td>
<td>6.7</td>
<td>3.2</td>
<td>4.7</td>
<td>2.7</td>
<td>6.1</td>
<td>4.2</td>
<td>3.4</td>
<td>3.3</td>
<td></td>
</tr>
</tbody>
</table>

ORR, Objective Response Rate; OS, Overall Survival; TTP, Time To Progression; D, Docetaxel; 5FU, 5Fluorouracil; MMC, Mytomicin C; G, Gemcitabine; MTX, Methotrexate; VLB, Vinblastine; X, Capecitabine; P, Paclitaxel.

**Table 3.** Trastuzumab in combination with a taxane

<table>
<thead>
<tr>
<th>Outcome</th>
<th>H+P</th>
<th>P</th>
<th>H+D</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>49</td>
<td>17</td>
<td>61</td>
<td>34</td>
</tr>
<tr>
<td>TTP (months)</td>
<td>7.1</td>
<td>3</td>
<td>11.7</td>
<td>6.1</td>
</tr>
<tr>
<td>OS (months)</td>
<td>24.8</td>
<td>17.9</td>
<td>31.2</td>
<td>22.7</td>
</tr>
</tbody>
</table>

H, Trastuzumab; P, Paclitaxel; D, Docetaxel.

**Her2-positive metastatic breast cancer**

Before 1998 specific treatment was not available for Her2-positive metastatic breast cancer; over the last few years the major breakthrough in cancer therapy was the possibility of to use, in this subset of patients, trastuzumab, a humanised monoclonal antibody that targets the human epidermal growth factor receptor-2 (Her2).

For optimal patient management, an accurate Her2 testing is essential. Trastuzumab should only be used in patients whose tumours have either Her2 overexpression or Her2 gene amplification as determined by an accurate and validated assay; IHC for Her2 receptor overexpression and/or FISH/CISH for Her2 gene amplification. In particular, the tumour with IHC 3+, or IHC2+ and FISH positive responds to trastuzumab [25–27].

Trastuzumab as monotherapy is an active and well-tolerated regimen, especially for patients unfit for chemotherapy, or not wanting to receive chemotherapy, or wishing to delay chemotherapy. As single agent in first line therapy of Her2 overexpressing metastatic breast cancer, trastuzumab produces about 35% of objective response rate [28].

Preclinical data showed consistent synergistic interactions of this antibody with a number of chemotherapeutic agents including docetaxel, vinorelbine, cisplatin, carboplatin, cyclophosphamide, gemcitabine, non-doxorubicine anthracyclines. These data accounted for several clinical trials of trastuzumab in combination with chemotherapy.

Two randomised trials validated trastuzumab in association with a taxane.

In the Slamon study the addition of the monoclonal antibody to chemotherapy, with AC or Paclitaxel regimen, determined an advantage of about 7 months in overall survival for the patients with IHC 3+ metastatic disease treated with the taxane plus trastuzumab [25]. This early result has validated in the Marty’s study where patients treated with the association of trastuzumab plus docetaxel gained 8.4 months in overall survival compared with the patients who receive docetaxel as single agent [29].

Survival results, but also significantly higher objective response rate, time to disease progression and maintenance of tumour response, of these two studies, validated first line use of trastuzumab with a taxane, paclitaxel or docetaxel, as a standard therapy for all patients with Her2-positive metastatic breast cancer (Table 3).

However, an interesting retrospective analysis in the subset of patients of the Slamon’s phase III trial who did not experience an objective clinical response after the treatment, showed a benefit from the addition of trastuzumab to chemotherapy also in stable patients, as demonstrated by a statistically significant improved time to progression (4.1 versus 2.8 months, P = 0.0027), and a trend towards improved overall survival in patients with FISH-positive disease [30].
the previous treatments

Now, most patients with a diagnosis of advanced breast cancer present having received a previous adjuvant treatment. The adjuvant chemotherapy is particularly important for the choice of the optimal first chemotherapeutic approach to advanced disease.

In fact, if the patient received a CMF-like (cyclophosphamide plus methotrexate plus 5-fluorouracil) regimen as adjuvant therapy, she will receive an anthracycline and/or taxane regimen based as first line chemotherapy. However, if the patient received an anthracycline-containing regimen in the adjuvant setting, can receive again the same schedule provided a long relapse-free interval has passed and a low cumulative anthracycline’s dose has administered (doxorubicin <450–550 mg/m² and epirubicin <700–900 mg/m²).

The relationship between the activity of first line chemotherapy for metastatic breast cancer and prior adjuvant treatment is controversial, since some studies showed a poorer outcome [31–34], whereas others demonstrated an outcome similar to patients who had not received previous adjuvant therapy [35–38].

A recent analysis evaluating the impact of adjuvant chemotherapy with anthracyclines on the outcome of 291 patients treated with the combination of epirubicin and paclitaxel at time of relapse, demonstrated a high level of activity of these drugs, either in combination or sequence, with an overall response rate of 66%, regardless of previous adjuvant therapy [39].

About the patients with a Her2-positive metastatic breast cancer, it is important to consider that the increasing use of the taxanes in the adjuvant, and neoadjuvant setting, will impact on treatment options of advanced disease, so the alternative effective options are required for patients who received a previous regimen with a taxane.

In vitro data that show a consistent synergistic interaction of trastuzumab with a lot of chemotherapeutic agents, and the differing chemotherapy profiles, and suggested to test, in many phase II studies, the activity of several promising trastuzumab regimens.

Interesting results have been obtained with the association of vinorelbine and trastuzumab. Highly-active and well-tolerated, this combination showed, in different phase II trials, an objective response rate that ranges from 38 to 86% [40, 41].

duration of therapy

The optimal treatment duration for patients with responsive or stable disease has been studied by several groups. For patients who achieve a complete response to initial therapy, two randomized trials have shown a prolonged disease-free survival from immediate treatment with a different chemotherapy regimen compared to observation with treatment upon relapse [42, 43]. Neither of these studies showed an improvement in overall survival for patients who received immediate treatment and in Peter’s study, survival was actually worse in the immediately treated group. However, no difference in overall survival was noted when patients with partial response or stable disease, after initial therapy, were randomized to receive either a different chemotherapy versus only observation [44] or a different chemotherapy regimen given at higher versus lower doses [45]. These data support the idea that different combination regimens of additional chemotherapy immediately following a patient’s best response to an induction chemotherapy regimen does not improve overall survival. At the last ASCO meeting were presented the final results from the Italian MANTA 1 study [46]. This clinical trial not showed any difference in progression free survival and overall survival with a maintenance regimen of paclitaxel every 3 weeks versus only control in patients with advanced breast cancer not progressing after first line anthracycline-paclitaxel based combination regimen.

conclusions

Because of high number of ‘old’ and ‘new’ chemotherapeutic agents, a wide spectrum of options is now available for metastatic breast cancer patients. Possibilities of prolonging survival and/or palliating symptoms are to be considered and balanced with the side effects (polychemotherapy versus monochemotherapy, peculiar toxic profile of each agent), the patient presentation (PS, pretreatments, symptoms, etc.) and the patient’s preference.

disclosures

Dr Pronzato has indicated no financial relationships with companies whose products are mentioned in this article.

references


