EJC SUPPLEMENTS 6, NO. 8 (2008) 1–4

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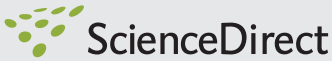

The 2007 Rome Forum on the Treatment of Breast Cancer: first-line treatment choices for metastatic breast cancer in Europe

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ARTICLE INFO

Keywords:
Metastatic breast cancer
Hormone receptor
HER2

1. Introduction

The prognosis of breast cancer patients has improved significantly in the last few years, mainly because of early diagnosis, better molecular classification of patients and more efficacious adjuvant therapies. A variety of new cytotoxic and targeted agents are available for treating metastatic breast cancer (MBC), some of which are already available in clinical practice, allowing therapy to be tailored to individual patients. Even in advanced disease, prolonged survival and a meaningful quality of life can be achieved in the majority of patients.[1–3] Major drivers of treatment choices in MBC are the molecular subtypes, prior exposure to adjuvant therapies, tumour extent and size and patient choice.

On 9 November 2007, key European opinion leaders in the field of breast cancer convened at the Rome Forum on the Treatment of Breast Cancer to discuss how first-line treatment choices for MBC are changing in Europe. This supplement contains the proceedings of this meeting summarised into the key presentation and discussion topics.

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2. New treatments for metastatic breast cancer

Identification of the molecular subtype of MBC is important for prognosis and for choosing the optimal therapeutic strategy. On the basis of hormone receptor (HR) status and human epidermal growth factor receptor (HER)2 status, four different subtypes of cancers can be identified: HER2-positive/HR-positive, HER2-positive/HR-negative, HER2-negative/HR-positive and HER2-negative/HR-negative. The appropriate management of these different tumour subtypes include the use of targeted agents, hormonal therapy, chemotherapy and loco-regional treatments. This multimodality approach has the potential to extend the chronic phase of metastatic disease and, at least for a subset of patients, there is the possibility that the patient can be cured, even in the presence of metastatic disease.

2.1. *HER2-positive/HR-positive cancer*

Approximately 15–20% of breast cancer patients have tumours with both HER2 and HR expression. These tumours are characterised as aggressive, with sensitivity to endocrine agents, chemotherapy and anti-HER2 agents.

New treatment approaches in this subset of patients have involved the combination of trastuzumab with endocrine agents. In the TAnDEM trial, anastrozole

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with or without trastuzumab was administered to 208 patients and it was found that the combination significantly increased time to disease progression, response rate and progression-free survival (PFS).[4] Even in the combination arm median PFS was extremely short (median PFS 4.2 months), demonstrating that these tumours are characterised by an aggressive outcome and poor endocrine responsiveness and, therefore, should be considered for treatment with chemotherapy plus trastuzumab upfront. However, approximately 20% of the patients treated with anastrozole and trastuzumab had disease that did not progress at 24 months and was associated with a significant delay in the need for subsequent chemotherapy.

Additional information (extent and site of metastatic spread, prior adjuvant therapies, more refined biological characterisation of the tumour) is necessary to improve identification of the subset of patients who are most likely to benefit from combined aromatase inhibitor plus trastuzumab therapy.

2.2. HER2-positive/HR-negative cancer

HER2-positive, HR-negative cancers represent approximately 10–15% of patients. These tumours are associated with an aggressive course of disease, including development of visceral and central nervous system (CNS) metastases, and are quite sensitive to chemotherapy,[5,6] in particular anthracycline- and taxane-based regimens and anti-HER2 agents. The combination of a taxane (either paclitaxel or docetaxel) with trastuzumab represents the standard treatment.[5,6]

A couple of randomised trials have demonstrated that the addition of carboplatin to a combination of trastuzumab plus a taxane (either paclitaxel or docetaxel) does not produce a greater benefit than trastuzumab plus a taxane alone. A trial from US Oncology (Houston, TX, USA) randomised patients to trastuzumab (2 mg/kg on days 1, 8 and 15) plus paclitaxel (175 mg/m^2 on day 2) with or without carboplatin (6 mg/mL/minute on day 2). The triplet combination was superior in terms of objective response rate ($p = 0.04$) and time to progression ($p = 0.03$), whereas the median overall survival was not significantly different between arms.[7] However, the more recent BCIRG (Breast Cancer International Research Group) trial randomised patients to trastuzumab plus docetaxel with or without carboplatin and demonstrated no advantage in terms of activity and efficacy for the addition of carboplatin to trastuzumab plus docetaxel.[8]

Treatment for patients with trastuzumab failure was investigated in a trial comparing the combination of capecitabine (2000 mg/m^2/day every 3 weeks) and lapatinib (1250 mg four times a day continuously) with capecitabine alone (2500 mg/m^2/day on days 1–14 every 3 weeks).[9] The combination was superior in terms of objective response rates ($p = 0.017$) and also in terms of median time to disease progression ($p = 0.00013$), but there was no difference in overall survival between the two treatment arms. Another interesting observation from this study was that the incidence of CNS metastases was significantly lower in the combination arm than in the single-agent arm.

Lapatinib alone or in combination with capecitabine can be effective for CNS metastases. Lin et al. presented data at the 2007 American Society of Clinical Oncology (ASCO) Breast Cancer Symposium on patients with CNS metastases after trastuzumab treatment and radiation therapy treated with lapatinib monotherapy (750 mg twice a day), and in the case of progressive disease, lapatinib (1250 mg/day) plus capecitabine (1000 mg/m^2 twice daily).[10] Of the patients in the lapatinib plus capecitabine extension arm, 20% achieved an objective response and 20% achieved significant tumour shrinkage of <50%.

Another active agent for HER2-positive patients is pertuzumab, an antibody directed against a different region of the extracellular domain of the HER2 receptor to trastuzumab. Baselga et al. presented data at the 2007 ASCO Breast Cancer Symposium demonstrating that patients with disease progression with the trastuzumab plus pertuzumab combination achieved an objective response in 18% of cases, with 20% achieving stable disease.[11]

2.3. HER2-negative/HR-positive cancer

The HER2-negative, HR-positive phenotype represents approximately 40–50% of MBCs. Patients with this phenotype have a rather indolent course of disease with prevalent bone and soft-tissue metastases. These tumours are sensitive to endocrine manipulation, but have a lower sensitivity to chemotherapy. These patients are usually treated with multiple lines of endocrine agents until development of endocrine resistance. Once chemotherapy has to be used, single agents are preferable because of the indolent course of the disease. Aromatase inhibitors have proven their efficacy and their superiority over tamoxifen and megestrol acetate, and have shown a disease-free survival benefit over other endocrine therapy in a combined analysis of randomised trials.[12]

2.4. HER2-negative/HR-negative cancer

'Triple-negative' cancers that do not over-express HER2, the oestrogen receptor or the progesterone receptor represent approximately 20% of the breast cancer patient population. Such tumours tend to be very aggressive, with a high tendency to develop visceral metastases. Endocrine-based therapies and anti-HER2 agents are not useful for these patients and, unfortunately, a number of patients have highly chemoresistant disease.

The majority of patients are treated with anthracycline adjuvant therapy, and in the setting of failed adjuvant anthracycline therapy there are two treatments that have shown superior efficacy in combination with a taxane compared with single-agent treatment: capecitabine and gemcitabine. In the first article in this supplement, Dr Miles discusses capecitabine both as a single agent and as part of a combination treatment. The second article, by Dr Colomer, covers the role of gemcitabine in combination therapy for first-line MBC. Another combination showing benefit in this patient group is paclitaxel plus bevacizumab. The role of vascular endothelial growth factor in tumour development and the opportunity it presents for bevacizumab treatment is discussed in the article by Dr Heinemann.

In the setting of patients who have not responded to treatment with anthracyclines and taxanes, there are no trials as yet showing that any agent, when used as part of a combination versus as a single agent, is superior in terms of survival. However, there are two trials showing benefits for combinations in terms of PFS. The combination arm performed better than the single-agent arm in both a phase III trial of capecitabine plus ixabepilone versus capecitabine alone,[13] and in a phase III trial of gemcitabine plus vinorelbine versus vinorelbine alone.[14] However, the ixabepilone combination had significantly higher toxicity with regard to neuropathy and febrile neutropenia compared with single-agent therapy.

A new albumin-bound formulation of paclitaxel (260 mg) was compared with conventional paclitaxel in a phase III trial in MBC patients and was found to confer significantly higher response rates ($p = 0.001$) and a longer time to disease progression ($p = 0.006$).[15] Grade 4 neutropenia was also significantly lower in the albumin-bound paclitaxel arm ($p < 0.001$), although rates of grade 3 sensory neuropathy ($p < 0.001$) and vomiting and diarrhoea were higher.

3. Variations in European practice

Discussions from the Rome Forum on the Treatment of Breast Cancer revealed that, based on the sample of doctors who attended, approximately 50% of MBC patients in Europe receive doublet combinations. However, there is still great variability between individual countries regarding which particular treatments are used, mainly as a result of regulatory and funding differences. In particular, France and Germany were found to use the paclitaxel plus bevacizumab combination outside clinical trials more than other European countries. It was also found that many MBC patients receive as many as four or five lines of therapy, and in these circumstances the benefits in efficacy from new treatments may be difficult to evaluate.

Acknowledgements

I would like to thank the authors for their valuable contributions to this supplement. Eli Lilly and Company is also gratefully acknowledged for supporting this supplement and for making its publication possible.

Conflict of interest statement

None to declare.

References

1. Giordano SH, Buzdar AU, Smith TL, et al. Is breast cancer survival improving? *Cancer* 2004;**100**:44–52.
2. Gennari A, Conte P, Rosso R, et al. Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. *Cancer* 2005;**104**:1742–50.
3. Guarneri V, Conte PF. The curability of breast cancer and the treatment of advanced disease. *Eur J Nucl Med Mol Imaging* 2004;**31**(Suppl 1):S149–61.
4. Mackey JR, Kaufman B, Clemens M, et al. Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer. *Breast Cancer Res Treat* 2006;**100**(Suppl 1) [abstract 3].
5. Slamon DJ, Leylan-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;**344**:783–92.
6. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005;**23**:4265–74.
7. Robert N, Leyland-Jones B, Asmar L, et al. Randomised phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol* 2006;**24**:2786–92.
8. Pegram M, Forbes J, Pienkowski T, et al. BCIRG 007: first overall survival analysis of randomised phase III trial of trastuzumab plus docetaxel with or without carboplatin as first line therapy in HER2 amplified metastatic breast cancer. *J Clin Oncol* 2007;**25**(20 Suppl) [abstract 1008].
9. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;**355**:2733–43.
10. Lin NU, Dieras V, Paul D, et al. EGF105084, a phase II study of lapatinib for brain metastases in patients (pts) with HER2+ breast cancer following trastuzumab (H) based systemic therapy and cranial radiotherapy (RT). *J Clin Oncol* 2007;**25**(20 Suppl) [abstract 1012].
11. Baselga J, Cameron D, Miles D, et al. Objective response rate in a phase II multicentre trial of pertuzumab (P), a HER2 dimerisation inhibiting monoclonal antibody, in combination with trastuzumab (T) in patients (pts) with HER2-positive metastatic breast cancer (MBC) which

has progressed during treatment with T. *J Clin Oncol* 2007;**25**(20 Suppl) [abstract 1004].
12. Gibson LJ, Dawson CK, Lawrence DH, Bliss JM. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. *Cochrane Database Syst Rev* 2007;(1):CD003370.
13. Vahdat LT, Thomas E, Li R, et al. Phase III trial of ixabepilone plus capecitabine compared to capecitabine alone in patients with metastatic breast cancer (MBC) previously treated or resistant to an anthracycline and resistant to taxanes. *J Clin Oncol* 2007;**25**(18 Suppl) [abstract 1006].
14. Martín M, Ruiz A, Muñoz M, et al. Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. *Lancet Oncol* 2007;**8**:219–25.
15. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol* 2005;**23**:7794–803.