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Efficacy of biological agents in metastatic triple-negative breast cancer

Annalisa Bramati [a,*], Serena Girelli [a,1], Valter Torri [b,2], Gabriella Farina [a,1], Elena Galfrascoli [a,1], Sheila Piva [a,1], Anna Moretti [a,1], Maria Chiara Dazzani [a,1], Paola Sburlati [a,1], Nicla Maria La Verde [a,1]

[a] *Department of Oncology, Fatebenefratelli e Oftalmico, Corso di Porta Nuova, 23, 20121 Milan, Italy*
[b] *IRCCS – Istituto di ricerche farmacologiche Mario Negri, Lab of Methodology of Biomedical research, Department of Oncology, via La Masa 19, 20156 Milan, Italy*

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ABSTRACT

Metastatic triple-negative breast cancer (mTNBC) represents 15% of invasive breast cancers. Prognosis is poor, and there is no specific target therapy but biological agents combined with chemotherapy may be effective.

To assess the role of biological agents in metastatic triple-negative breast cancer we performed a systematic review of phase III randomized controlled trials published from January 2006 to February 2013 and presentations at ESMO, ASCO, and SABCS congresses in 2010–2012. We consulted PubMed and ClinicalTrials.gov. Only studies comparing biological agents and chemotherapy versus chemotherapy alone were considered. Relevant statistical variables were log of the hazard ratio and relative variance for progression-free survival (PFS) and overall survival (OS).

Of 353 PubMed publications and 229 studies registered on ClinicalTrials.gov, 10 trials were selected and 5293 patients were analyzed: 1546 had mTNBC. Biological agents considered were bevacizumab, sunitinib, sorafenib, lapatinib, iniparib and cetuximab. In addition, a meta analysis of the four studies containing bevacizumab was performed and it showed a PFS improvement with a relative risk reduction of 35% (95% CI: 25–43%). No effect on OS was observed. No PFS and OS benefit was detected with the other agents.

No improvement of OS was detected in patients treated with biological agents plus chemotherapy, while a significant PFS improvement was observed only for bevacizumab and cetuximab. The overall impact of these agents on patient survival was not as great as expected, probably because the molecular basis of this illness needs to be better understood so that treatment can be more appropriately tailored.

Introduction

“Triple-negative” breast cancer (TNBC) has been identified for biological characteristics and clinical outcome as a separate disease in the last few years. It is characterized by the presence of triple-negative immunohistochemistry for estrogen receptors (ER), progesterone receptors (PgR), and the HER-2 gene [1]. TNBC represents about 15% of all cases of breast cancer and occurs more frequently in young and African American women; it is considered to be a subtype of basal-like disease, which has great variability of expression [2–5]. Several studies have demonstrated that the prognosis in this setting is poor [6,7].

TNBC often occurs in patients carrying BRCA-1 and -2 mutations [8]. Although the majority of patients with immunohistologically defined TNBC do not have BRCA-1 and -2 mutations, it is possible that mutations in other DNA repair pathway genes could be involved in the development of cancer.

Cisplatin and its derivatives bind to and cause cross-linking of DNA during replication, thus interfering with cell division. Without effective DNA repair mechanisms, these compounds cause cell death by apoptosis. Neo-adjuvant studies have demonstrated the efficacy of cisplatin in vivo, although most studies of cisplatin in a metastatic setting have been retrospective [9,10]. Taxanes as well as ixabepilone and anthracyclines, have also been shown to be active in this setting [11].

Molecular biology is a cornerstone in modern oncology, and cellular pathways are being explored to identify strategic checkpoints

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[*] Corresponding author. Tel.: +39 02 6363 2223; fax: +39 02 6363 2216.

E-mail addresses: annalisa.bramati@fbf.milano.it (A. Bramati), datamanager@fbf.milano.it (S. Girelli), valter.torri@marionegri.it (V. Torri), gabriella.farina@fbf.milano.it (G. Farina), elena.galfrascoli@gmail.com (E. Galfrascoli), sheila.piva@fbf.milano.it (S. Piva), anna.moretti@fbf.milano.it (A. Moretti), chiara.dazzani@fbf.milano.it (M.C. Dazzani), paola.sburlati@fbf.milano.it (P. Sburlati), nicla.laverde@fbf.milano.it (N.M. La Verde).

[1] Tel.: +39 02 6363 2223; fax: +39 02 6363 2216.

[2] Tel.: +39 02 39014528; fax: +39 02 39014522.

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that can be targeted by new drugs. Among these pathways, the DNA repair system is now well defined. It is known that DNA repair mechanisms are based on gene redundancy; if one of the two copies of the gene is damaged, the other copy will be activated to work instead of the damaged one.

In many patients with breast cancer who have familial or sporadic mutations of DNA repair genes (e.g., BRCA-1 and -2), the homologous gene can be blocked by a specific agent, with subsequent cell cycle arrest and cell death; the hypothesis behind this mechanism is known as “synthetic lethality.” Based on this hypothesis, the activity and efficacy of PARP inhibitors have been studied in patients with BRCA-1 and -2 mutations [12].

Angiogenesis is also a target of new biological drugs. Multiple angiogenic factors are commonly expressed by invasive breast cancers; the 121-amino-acid isoform of vascular endothelial growth factor (VEGF) predominates. VEGF stimulates endothelial proliferation and migration, inhibits endothelial apoptosis, induces proteinases that remodel the extracellular matrix, increases vascular permeability and vasodilatation, and inhibits antigen-presenting dendritic cells. Differences in function among the various VEGF isoforms are not well defined, though VEGF-C has a predominant role in lymphangiogenesis, whereas VEGF-A is more potent in inducing vasodilatation and pathologic angiogenesis [13].

Bevacizumab is a humanized monoclonal antibody directed against all isoforms of VEGF-A that leads to normalization of the blood supply to cancerous cells.

In addition, neoplastic cells have multiple growth patterns that are regulated by the progressive activation of kinase enzymes. If a blockade in one of these pathways affects the cell, it can be overcome by a kinase associated with another pattern. In this setting, multikinase inhibitors, such as sunitinib and sorafenib, inhibit endothelial growth factors, PDGFR alfa and beta and protein kinases such as c-raf, b-raf, c-KIT, and flt-3 [14–16]. The discovery that these pathways are activated in breast cancer led to clinical studies with sorafenib and sunitinib.

The efficacy of sorafenib has been demonstrated in advanced renal cell and hepatocellular carcinomas. Sorafenib demonstrated limited activity as single-agent in metastatic breast cancer; so it was postulated that greater activity might be achieved by combining it with chemotherapy [17].

Sunitinib is an oral inhibitor of tyrosine kinase receptors implicated in breast cancer growth and metastasis, including vascular endothelial growth factor receptors, PDGFR, stem cell factor receptors, and colony-stimulating factor-1 receptors [18]. In preclinical studies involving the human breast cancer MX-1 xenograft model, sunitinib in combination with docetaxel, doxorubicin, or fluorouracil enhanced the antitumor activity of the chemotherapeutic agents, and the effect was accompanied by increased survival [19].

Epidermal growth factor receptor (EGFR) has been shown to be highly expressed in TNBC cell lines [20], which are inhibited by the anti-EGFR monoclonal antibody cetuximab.

At present, there are several ongoing studies to evaluate the efficacy of molecular targeting agents in patients with TNBC. The aim of the present study was to perform a systematic review and meta-analysis of the studies available to date in the literature, in order to improve treatment strategies in this subgroup of patients.

Materials and methods

Literature search strategy

For this systematic review, we searched for published randomized controlled clinical trials (RCTs) in the PubMed database from January 2006 to February 2013 that met the following inclusion criteria: (1) Phase II and III randomized clinical trials, fully published in scientific journals. (2) Designed to compare chemotherapy combined with a biological agent (BA) vs chemotherapy alone for the treatment of patients with metastatic breast cancer as first or subsequent lines of therapy. (3) Inclusion of a population of patients with TNBC or with the chance of extrapolating data to the subgroup of patients with TNBC.

The following terms were used in the search: triple negative AND breast cancer AND metastatic breast cancer AND chemotherapy.

We also considered ongoing clinical trials registered in the ClinicalTrials.gov database, as follows: (1) Phase II study AND breast cancer AND triple negative AND interventional study. (2) Phase III study AND breast cancer AND (bevacizumab OR sorafenib OR sunitinib OR erlotinib OR gefitinib OR iniparib OR olaparib OR cetuximab OR HDACI OR everolimus OR temsirolimus) AND interventional study.

Selection criteria

The efficacy of chemotherapy combined with a BA was considered. Outcome measures of interest included (1) progression-free survival (PFS), defined as the time from randomization until disease progression or death without disease progression or the date of the last follow-up for patients who were still alive without disease progression and (2) overall survival (OS), defined as the time from randomization until death from any cause or the date of the last follow-up for patients who were still alive.

For each study selected for the meta-analysis, we looked for published articles or abstracts. For unpublished articles, we looked for oral presentations at 2010–2012 conferences such as the American Society of Clinical Oncology (ASCO), the San Antonio Breast Cancer Symposium (SABCS), and the European Society for Medical Oncology (ESMO).

The RCTs selected for the meta-analysis had to fulfill both of the following criteria: (1) Inclusion of patients with histologically confirmed breast cancer with distant metastasis. (2) Reported results for PFS and OS, both for the general population and for the triple-negative subgroup, which was randomized to receive chemotherapy alone or combined with the new drug.

Data extraction

Two oncologists from the Oncology Department of Fatebenefratelli and Oftalmico Hospital independently reviewed the literature, and the data were discussed with a supervising statistician from the Oncology Department of Mario Negri Institute in Milan. We created a database summarizing the number of patients in each arm of the studies and the number of patients with TNBC. With regard to efficacy endpoints, we reported the number of events for each arm with the respective hazard ratio value (HR), confidence interval (CI), and p value, with median PFS and OS.

Statistical analysis

For each trial, the HR and 95% CI for OS and PFS and the survival ratio of the group that received CT + BA vs the group without BA were retrieved. Natural log transformation of HR was used, and the standard error was calculated from the 95% CI if the HR was not provided in the original publication; natural log HR and its standard error were estimated by the indirect method, as described by Parmar et al. [21]. The heterogeneity among all trials and among predefined treatment subsets was assessed with a c2 test. If there was no heterogeneity among the studies, as confirmed by c2 test, these were selected for analyses. If the results of trials were heterogeneous, the effects of possible explaining factors were explored. A fixed-effect model was used to estimate the treatment