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Role of cytotoxics in combination with targeted agents

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ABSTRACT

Combining cytotoxics with targeted agents can lead to enhanced efficacy in metastatic breast cancer (MBC). Cytotoxic/targeted agent combinations approved for the treatment of MBC include trastuzumab plus paclitaxel or docetaxel for the first-line treatment in patients presenting with HER2-positive breast cancer. Furthermore, in HER2-negative disease combining bevacizumab with paclitaxel for the first-line treatment of HER2-negative patients is superior compared to monotherapy with either drug. Lapatinib plus capecitabine recently received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for conditional marketing authorisation in patients with HER2-positive breast cancer following prior therapy with anthracyclines, taxanes and trastuzumab. The novel epothilone ixabepilone is also under investigation in this setting. Preclinical studies have demonstrated synergistic activity in combination with targeted agents including trastuzumab and bevacizumab and early clinical studies have revealed encouraging response rates in combination with trastuzumab and carboplatin in patients with HER2-positive MBC. This article will review recent data on the efficacy of combining cytotoxics with targeted agents for the treatment of MBC.

1. Introduction

Treatment decisions for combined treatment modalities in MBC should be based on one of three overriding principles: each agent should have demonstrated single-agent activity with no cross-resistance to other potential components of the regimen; the proposed agents should have demonstrated synergistic effects; and the tolerability profiles of the proposed agents should not overlap. [1] Older combination regimens were largely selected on an empirical basis and rarely met these basic requirements for a rational combination regimen. As a consequence, single-agent sequential chemotherapy has been the preferred treatment paradigm for the management of metastatic breast cancer (MBC) until relatively recently, largely as a consequence of the additive side effects and the unacceptable impact on quality of life using older combination regimens for an end-of-life patient group.

In recent years, new combination chemotherapy regimens, particularly with newer cytotoxic agents, have gained increasing attention as a valuable treatment option for patients with MBC, with evidence emerging for prolonged progression-free periods with regimens comprising novel cytotoxic agents including gemcitabine. [2] or the novel epothilone, ixabepilone. [3]

The emergence of novel agents directed towards specific molecular targets and lesions associated with breast cancer and new cytotoxic agents such as the epothilones, a novel group of microtubule-stabilising agents, has further expanded the array of drugs available for combination therapy regimens. Targeted agents approved or under evaluation in the MBC setting include trastuzumab (a human epidermal growth factor receptor 2 [HER2]-targeted monoclonal antibody), bevacizumab (a vascular endothelial growth factor [VEGF]-targeted antibody) and lapatinib (a HER1- and HER2-targeted tyrosine kinase inhibitor).

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This paper reviews recent data on the efficacy of combining established and novel cytotoxic agents with targeted agents for the treatment of MBC.

2. Established cytotoxic/targeted combination regimens

There are currently a number of cytotoxic/targeted agent combinations approved for the treatment of MBC.

2.1. First-line therapy

Trastuzumab plus paclitaxel or docetaxel is currently approved for the first-line treatment of HER2-positive patients. The efficacy of this combination has been consistently demonstrated in a series of phase III trials. The addition of trastuzumab significantly improved patient outcomes such as response rate and time to progression (TTP) in patients with HER2-positive MBC. In combination with docetaxel, the addition of trastuzumab extended TTP from 6.1 months to 11.7 months ($P = 0.001$). [4] Similarly, when combined with docetaxel, trastuzumab extended TTP from 3.0 months to 6.9 months among previously-treated MBC patients, [5] and from 7.3 months to 10.8 months in the first-line treatment of HER2-positive MBC. [6]

Bevacizumab plus paclitaxel is approved for the first-line treatment of HER2-negative patients. In the pivotal clinical trial, bevacizumab plus paclitaxel therapy significantly prolonged progression-free survival (PFS; 11.8 vs 5.9 months; $P < 0.001$) and overall response rate (36.9% vs 21.2%; $P < 0.001$) compared with paclitaxel alone, but not overall survival (OS; $P = 0.16$). [7] The results from this study have recently been confirmed by an independent review of the data showing that bevacizumab has beneficial effects on PFS and response rate. [8]

2.2. Second-line therapy

The combination of lapatinib and the cytotoxic agent capecitabine has recently received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for conditional marketing authorisation in patients with HER2-positive breast cancer following prior therapy with anthracyclines, taxanes and trastuzumab. [9] A phase III trial has investigated the benefits of lapatinib plus capecitabine vs capecitabine alone in patients with HER2-positive MBC that had progressed after treatment with regimens that included an anthracycline, a taxane and trastuzumab. [9,10] The results demonstrated that the addition of lapatinib significantly prolonged median TTP from 4.3 to 6.2 months (hazard ratio [HR] 0.57; 95% CI: 0.43–0.77; $P < 0.001$) without compromising tolerability. Although combination therapy did not increase the incidence of symptomatic cardiac events (such as declines in left ventricular ejection fraction), diarrhoea and rash were reported more frequently in the lapatinib plus capecitabine group.

3. Investigational cytotoxic/targeted combination regimens

A number of cytotoxic/targeted combinations are currently under investigation.

3.1. Bevacizumab plus chemotherapy

A study evaluating the combination of bevacizumab plus capecitabine has provided encouraging preliminary results. [11] In this ongoing study, patients with HER2-negative disease are initially treated with bevacizumab plus capecitabine. On progression, patients are then switched to receive bevacizumab plus other chemotherapy. After a median follow-up of 12.9 months, the median TTP was 5.7 months and the median OS 16.0+ months. Notably, in this study outcomes (median TTP, median OS and overall response rates) were approximately doubled for those patients with oestrogen receptor-positive disease compared with those who were oestrogen receptor-negative. [11]

Results from the AVADO trial have recently been presented. [12] In this study of approximately 700 women with locally recurrent or metastatic breast cancer, bevacizumab in combination with docetaxel significantly improved PFS (8.7 [bevacizumab 7.5 mg/kg] and 8.8 [bevacizumab 15 mg/kg] vs 8.0 months for docetaxel alone; $P = 0.0318$ and $P = 0.0099$, respectively) and response rate (55% [bevacizumab 7.5 mg/kg] and 63% [bevacizumab 15 mg/kg] vs 44% for docetaxel alone; $P = 0.0295$ and $P = 0.0001$, respectively). Overall findings did not reveal any new safety signals with combination therapy. [12]

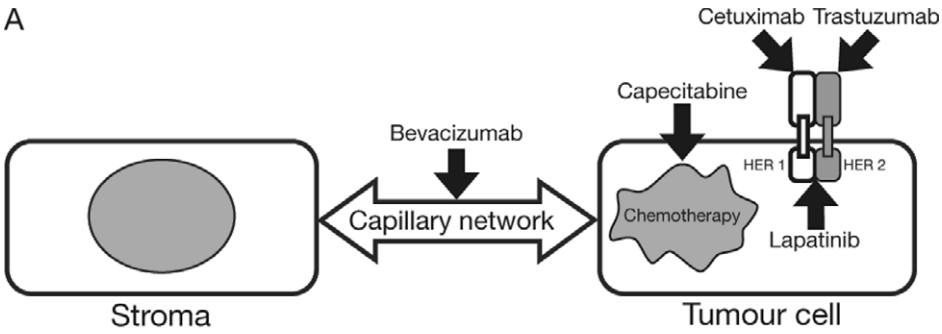
3.2. Lapatinib plus chemotherapy

Combination therapy with lapatinib plus paclitaxel in patients with HER2-negative disease has recently been a subject of evaluation. [13] In this study of combination therapy as first-line treatment of patients with MBC, lapatinib plus paclitaxel achieved a median TTP of 6.25 months and an overall response rate of 30%. The most common adverse events (all grades) in this study were alopecia (58%), neurological (55%, of which 8% were grade 3), diarrhoea (42%, of which 3.9% were grade 3), nausea (32%) and rash (32%). Neutropenia was reported in 18% of patients.

4. Novel cytotoxics in combination with targeted agents

Current evidence supports the efficacy of targeted therapies as part of combination regimens for the first-line treatment of MBC. Nevertheless, cytotoxic chemotherapy remains the backbone of treatment for MBC and there is an urgent need for newer cytotoxic agents that offer improved outcomes to those patients

A



B

Study		Phase	N	Endpoints
CA163-140	Ixabepilone + trastuzumab vs docetaxel + trastuzumab first-line in HER2 + LABC or MBC	II	80	ORR, PFS, response duration, time to response, safety
NCI-6297	Ixabepilone + trastuzumab first-line in HER2+ MBC	II	60	ORR, Safety, toxicity, TTP, TTF, correlation biomarkers with response
CA163-115	Three-arm trial of two schedules of ixabepilone + bevacizumab and paclitaxel + bevacizumab first-line therapy for HER2– LABC or MBC	II	120	ORR, response duration, time to response, PFS, OS
CA163-139	Ixabepilone and ixabepilone + cetuximab first-line therapy in triple-negative MBC	II	80	ORR, PFS, duration/time to response
CA163-144	Ixabepilone + lapatinib vs ixabepilone + lapatinib + capecitabine in pretreated HER2+ LABC or MBC	II	60	MTD, PK, safety, ORR, response duration

Fig. 1 – (A) Highlighting the cellular targets for key agents. (B) Trials investigating the effects of combination therapy with ixabepilone in the treatment of MBC.

who fail to respond to standard chemotherapy regimens and that can be combined with targeted agents.

The novel microtubule-stabilising agent ixabepilone (an epothilone B analogue) has demonstrated preclinical synergy with a number of targeted agents including trastuzumab and bevacizumab.[14,15] and is currently undergoing clinical evaluation in combination with trastuzumab and carboplatin.[3] Additional information concerning other trials with ixabepilone in various breast cancer populations (e.g. taxane resistant and advanced disease) is provided in the accompanying article by Pierre Fumoleau.[16]

The effects of adding ixabepilone to trastuzumab and carboplatin in patients with HER2-positive MBC have recently been investigated in a phase II study.[3] Patients were excluded from the study if they had received trastuzumab in the metastatic setting; however, adjuvant therapy with trastuzumab was permitted. Patients received three treatment cycles before being assessed for response, three further treatment cycles, and then, following a second response assessment, continuation therapy with trastuzumab. The results were comparable to those of studies investigating taxane-based regimens with an objective response rate of 44%, and 24% of patients achieving stable disease lasting $\geqslant$6 months. The median PFS was 8 months and the combination was well tolerated. Several ongoing clinical trials are currently investigating the effects of ixabepilone in combination with various cytotoxic and targeted agents for the treatment of MBC (Fig. 1). These include:

- a phase II trial comparing the effects of trastuzumab in combination with ixabepilone or docetaxel as first-line therapy in patients with HER2-positive, locally advanced or metastatic breast cancer (study CA163-140; study code: NCT00490646);
- a phase II study in which the combination of ixabepilone plus trastuzumab is being evaluated in two separate cohorts for the first-line therapy of patients with HER2-positive MBC. The first cohort contains patients previously treated for MBC with chemotherapy and trastuzumab while patients in the second cohort have received only hormone therapy in the metastatic setting (study NCI-6297; study code: NCT00079326);
- a phase II study comparing two regimens of ixabepilone plus bevacizumab and a third regimen of paclitaxel plus bevacizumab in patients with HER2-negative locally advanced or metastatic breast cancer who have received no prior chemotherapy (study CA163-115; study code: NCT00370552);
- a phase II study evaluating ixabepilone compared with ixabepilone plus cetuximab in triple-negative MBC (study CA163-13; study code: NCT00633464);
- a phase I study comparing ixabepilone plus lapatinib with ixabepilone plus lapatinib and capecitabine in pre-treated patients with HER2-positive locally advanced or metastatic breast cancer (study CA163-144; study code: NCT00634088).

5. Conclusions

Combining cytotoxic and targeted therapies has proved effective for the first-line treatment of MBC. A number of

such novel combinations that have been shown to offer improved response rates and prolonged progression-free periods compared with single-agent chemotherapy have now received approval for use in this setting. However, chemotherapy continues to be the backbone for combination therapy of MBC and there is a continuing need for novel chemotherapeutics that can overcome the resistance mechanisms that compromise the use of established agents including the anthracyclines and taxanes.

The novel epothilone ixabepilone provides beneficial effects even after prior therapy with taxanes and anthracyclines. Preclinical data have demonstrated positive synergistic effects in combination with a number of targeted agents, and early clinical data have indicated response rates comparable with those reported for taxane-based regimens and encouraging PFS rates.[3] On this basis a number of studies are ongoing that will provide data on the efficacy of ixabepilone in combination with targeted agents for the treatment of MBC as an alternative first-line treatment regimen.

Until relatively recently, treatment options for patients with MBC facing the last weeks and months of their life have been tremendously limited. Accumulated drug resistance as a consequence of prior exposure to the most effective established chemotherapeutics has continued to drive the search for novel cytotoxics and novel targeted agents to enhance the beneficial effects of therapy with the hope of prolonging life while maintaining quality of life. The emergence of targeted therapies and new cytotoxic agents such as ixabepilone continues to expand the armamentarium for the rational selection of combination regimens in the treatment of MBC.

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