available at www.sciencedirect.com

ScienceDirect

The role of new cytotoxic agents for the treatment of metastatic breast cancer

*PierFranco Conte**

Department of Oncology and Hematology, University Hospital, Modena, Italy

1. Introduction

Despite recent advances in targeted therapies for breast cancer, the need for new treatment options clearly remains. One area of interest is the role of novel cytotoxic agents.

A well attended BMS-sponsored symposium was held at the ESMO meeting in Stockholm, 2008. The aim of the symposium was to provide an outline of the latest data surrounding the use of cytotoxic agents for the treatment of metastatic breast cancer. The content of the symposium forms the basis of the supplement presented here, and each article is authored by one of the four speakers in Stockholm.

Given the level of interest and attendance during the symposium itself, the speakers were all keen to promote the evaluation of 'new' chemotherapy options. We hope that this supplement provides some key background information, stimulates discussion, and provides our insight as to some of the current issues faced by oncologists in 2009.

2. Mechanisms and consequences of chemotherapy resistance

Resistance to chemotherapy is a substantial clinical problem as it limits the effectiveness of anticancer drug treatment. Indeed, as Dr Coley points out, primary chemotherapy resistance can occur in up to 30–40% of the patients with metastatic breast cancer and, eventually, all these patients will experience treatment failure. Chemoresistance affects a number of drug classes used in first-line therapy including anthracyclines and taxanes. Several mechanisms underlie chemoresistance and these may be particularly relevant in the treatment of breast cancer. It is important, as clinicians, that we have an understanding of these different mechanisms. Dr Coley provides this background information.

Treatment approaches to reverse multi-drug resistance have met with limited success. Targeted agents, such as trastuzumab, can have synergy with chemotherapy in subgroups of patients, e.g. those with HER2 positive disease. In addition, agents such as the epothilones, which have low susceptibility to some of the common types of drug resistance, have demonstrated activity in taxane-resistant breast cancer.

3. Treatment beyond taxanes, emerging new cytotoxic agents

Until recently, taxanes were considered the first choice of therapy for patients with metastatic breast cancer. Unfortunately, as outlined by Dr Coley, the clinical utility of the taxanes for breast cancer is limited in some patients by the emergence of drug resistance. Several agents (e.g. capecitabine, vinorelbine, gemcitabine) have all demonstrated activity in patients with taxane-pretreated or -refractory metastatic breast cancer.

Professor Fumoleau reports that agents such as the epothilones have shown promising activity in patients with metastatic breast cancer, including patients resistant to taxanes and other cytotoxic drugs. The epothilones are microtubule-stabilising agents with a different mechanism of action than taxanes. Currently, three epothilone B synthetic derivatives – ixabepilone (BMS-247550), patupilone (EPO906), sagopilone (ZK-EPO) – and an epothilone D derivative (KOS-1584) are in development. Studies are currently ongoing to evaluate the epothilones compared with taxane regimens and to assess them when used as part of a combination therapy.

* Correspondence: PierFranco Conte.
Tel: +39 059 4224538; Fax: +39 059 4224429.
E-mail address: conte.pierfranco@unimore.it (P. Conte).

1359-6349/ $ – see front matter

4. Triple-negative patients: current options and future management

Triple-negative disease is a particularly difficult-to-treat and biologically aggressive breast cancer subgroup that does not respond to trastuzumab and hormonal treatments. For patients with triple-negative breast cancer there is a lack of specific treatment guidelines, and they are typically managed with standard therapies. Although there are limited treatment options and there is little data on which to base treatment decisions, there is evidence to suggest that some patients with triple-negative tumours may have increased sensitivity to chemotherapy.

Optimising existing chemotherapeutic regimens (i.e. using combinations or dose-dense treatments) may be the answer when treating triple-negative breast cancers. But we should not restrict ourselves to these options; new agents and approaches are also needed. These include the epothilones, targeted agents and the PARP inhibitors. New data are expected to emerge in the next few years which may lead to improved prognosis for this hard-to-treat patient group.

5. Role of cytotoxics in combination with targeted agents

Professor Jackisch discusses the rationale for combining cytotoxic and targeted agents and highlights that there are currently a number of cytotoxic/targeted combinations approved for the treatment of metastatic breast cancer.

Ixabepilone has demonstrated preclinical synergy with a number of targeted agents including trastuzumab and bevacizumab. A recent study investigated a combination of ixabepilone, trastuzumab and carboplatin in patients with HER2-positive metastatic breast cancer who had not received prior chemotherapy regimens. The combination was well tolerated and the observed response rate was similar to that of taxane regimens in combination with these agents. Studies are now ongoing to investigate ixabepilone in combination with other targeted agents including trastuzumab, bevacizumab, and cetuximab.

6. Summary

Chemotherapy with agents such as the anthracyclines and the taxanes remains a mainstay of breast cancer treatment, however improvement on these therapies is clearly needed. It is important to achieve a greater clinical benefit not only in patients who have developed resistance to these agents, but also in key patient sub-populations who have the worst prognosis. The papers in this supplement do not just highlight the problems faced when treating these patient groups, but provide some hope for the improvements we can expect from future therapies, including new cytotoxics.

Acknowledgements: Medical writing and editorial assistance, provided by Gardiner-Caldwell U.S., was supported by Bristol-Myers Squibb.

Competing interests: Dr Conte has acted as consultant and speaker for Bristol-Myers Squibb.