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Introduction

The Role of Docetaxel in Improving Treatment Outcomes in Advanced Breast Cancer

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ADVANCED BREAST cancer is a major public health problem. Although most women in developed countries who develop breast cancer are diagnosed when the disease is operable, locally advanced or disseminated tumours account for more than half of new cases in developing countries. Despite optimal multidisciplinary management, approximately half of all patients with operable disease ultimately relapse. Many patients with metastatic breast disease have a prolonged chronic illness, with periods of reactivation and remission requiring multiple therapeutic approaches. This places a heavy burden on healthcare resources.

Although the past two to three decades have seen many advances in both endocrine and chemotherapeutic treatments, these developments have largely resulted in a reduction in toxicity rather than improved control of the disease and so advanced breast cancer remains incurable. Certain features such as liver metastases and resistance to chemotherapy contribute further to the poor prognoses of these patients. Thus, innovative approaches to treatment are urgently required.

The role of the taxoid docetaxel (Taxotere®) in the treatment of advanced breast cancer was discussed at a satellite symposium entitled 'Improving Treatment Outcomes in Advanced Breast Cancer', which took place at the 7th EORTC Breast Cancer Working Conference in Bordeaux, France, in September 1996. The key messages emerging from the symposium concerned the definition of anthracycline resistance and the promising activity of docetaxel.

Current definitions of anthracycline resistance differ widely. Clinical trials in which more stringent definitions are used when selecting patients with anthracycline-resistant tumours tend to show lower response rates to the anticancer agents being evaluated than do trials in which broader definitions are used. To interpret and compare the data from such trials and to be able to determine accurately which of these agents is the most effective, it is imperative that the definition of anthracycline resistance is consistent.

According to Aman Buzdar of The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA, the three broad subgroups of anthracycline resistance depend on patients' response to initial therapy and can be defined as follows:

(i) primary resistance (anthracycline refractory), when patients experience recurrence while on an anthracycline-based adjuvant therapy, or progressive disease while receiving such treatment;
(ii) progression of disease following discontinuation of anthracycline-based therapy (anthracycline resistant), with a short duration of response indicating resistance to therapy; and
(iii) stable disease (unchanging) while receiving anthracycline-based therapy.

Patients in each subgroup have different prognoses. The dose intensity of anthracycline is also important; patients treated previously with a suboptimal dose may be viewed as being anthracycline resistant, but they might respond if treated with higher doses [1]. The mechanisms described as being involved in anthracycline resistance include drug efflux pumps, expression of aberrant forms of topoisomerase II, changes in the glutathione free-radical system and abnormality in apoptotic mechanisms.

Docetaxel and paclitaxel have been shown to be active against anthracycline-resistant breast cancer, a response rate of 41% with docetaxel being reported [2, 3].

Although the prognosis for patients with liver metastases is usually poor, docetaxel achieves promising response rates in these patients. The median survival after starting chemotherapy for patients with metastatic disease is about 8 months, whereas those with liver metastases survive for an average of only 4.5 months [4]. According to Pierre Fumoleau (René Gauducheau Centre, Nantes, France), docetaxel gives an overall response rate of 61% and a response rate of 60% in patients with liver metastases were found in phase II studies in which docetaxel 100 mg/m^2 was used as first-line chemotherapy; the median length of survival was 14.7 months. Docetaxel was also found to be active against visceral disease, whether or not patients have received previous adjuvant therapy. These results suggest that docetaxel may be superior to other single agents in patients with liver metastases from breast cancer.

Novel first-line treatment schedules involving docetaxel are also being examined in trials in which it is combined with other drugs. Veronique Diéras (Curie Institute, Paris,

France) and Wim ten Bokkel Huinink (The Netherlands Cancer Institute, Amsterdam, The Netherlands) are investigating the use of docetaxel either in combination or in sequential high-dose chemotherapy regimens.

In summing up the presentations given at the symposium, Michel Marty of St Louis' Hospital, Paris, France, speculated on the future role of docetaxel in first-line treatment of advanced breast cancer. Whether docetaxel should be used in combination or in sequential regimens remains to be defined. In patients who have had prior exposure to anthracycline (up to 60% of patients in some European countries), docetaxel-based combinations with 5-fluorouracil, cyclophosphamide or vinorelbine may be the best treatment options available; further phase II and III trials should reveal which of these combinations is the most effective. The efficacy of docetaxel in accelerated chemotherapy regimens followed by consolidation and stem-cell support also needs to be evaluated.

In conclusion, docetaxel may provide a real advance in the treatment of breast cancer, both for improved quality of life and survival of patients with this disease.

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