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European Journal of Cancer 37 (2001) S1–S2

European Journal of Cancer

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Introduction

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Received 3 July 2000; received in revised form 7 September 2000; accepted 11 September 2000

Metastatic breast cancer is considered to be a chronic disease. Whilst prolonged disease control can be achieved using endocrine and/or chemotherapy, most patients will ultimately die due to their cancer. Optimal use of the different available treatment modalities should be considered to achieve maximal palliation and to delay disease progression and death with as little toxicity as possible.

For many patients, hormonal agents remain the initial therapy of choice. The introduction of specific hormonal treatments in place of ablative endocrine procedures has enhanced the tolerability and acceptability of this type of therapy; some patients responding to first-line treatment are capable of achieving second- and third-line responses. However, most patients will at some point require intervention with cytotoxic chemotherapy. The use of optimal doses of chemotherapy is now recognised as being of critical importance to patient response, although the benefits of high-dose chemotherapy remain unclear.

In recent years, increased understanding of the biology of breast cancer has led to the identification of a number of novel therapeutic targets. One such target is the human epidermal growth factor receptor-2 (HER2), which is a member of the HER *(erb*B or Type 1) tyrosine kinase growth factor receptor family, one of the best studied growth factor receptor systems in breast cancer. HER2 amplification/overexpression has been shown to occur in 20–30% of breast cancer patients and is associated with more aggressive disease and a worse prognosis [1–3]. Slamon and colleagues demonstrated that median survival from first diagnosis in patients with high HER2 expression is less than half that in patients with HER2-negative tumours (3 versus approximately 6–7 years, respectively) [1]. In addition, HER2-positive tumours may respond to certain types of cytotoxic agents and to hormonal therapy in a different manner to those that are HER2-negative [4].

Studies using breast cell lines that had been engineered to overexpress HER2 revealed that *HER2*-gene amplification and overexpression produce many of the features of malignant cells, including increased DNA synthesis, cell growth, anchorage-independent growth, tumorigenicity and metastatic potential [5,6]. These observations and the extracellular location of part of the receptor indicated that HER2 could be a target for specific therapy. Murine monoclonal antibodies (muMAbs) directed against the extracellular domain of the receptor were shown to inhibit the growth of HER2-overexpressing cell lines, but not of cells expressing normal amounts of the receptor [7–9]. The most effective of these muMAbs, designated 4D5, was subsequently shown to exert potent antitumour effects in murine xenograft models of human breast cancers overexpressing HER2 [10–12]. However, long-term clinical use of muMAb 4D5 was felt not to be feasible because repeated exposure of the human immune system to foreign proteins is known to result in the development of neutralising human antimurine antibodies.

This limitation stimulated research that resulted in the humanisation of muMAb 4D5. By replacing the structural sequences of muMAb 4D5 whilst conserving the antigen recognition sequences, the recombinant humanised anti-HER2 monoclonal antibody (rhuMAb HER2) Herceptin® (trastuzumab) was developed [11]. In preclinical studies, the humanised MAb was shown to be specific for the HER2 receptor, to inhibit cell proliferation and to support antibody-dependent cell-mediated cytotoxicity only against HER2-overexpressing cell lines [11]. Furthermore, trastuzumab suppressed human HER2-overexpressing tumour xenografts in mice [13].

Phase I clinical trials of single and multiple doses of trastuzumab (10–500 mg) both alone and in combination with cisplatin defined the pharmacokinetics of trastuzumab and demonstrated that a dose of 100 mg

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0959-8049/01/$ - see front matter
PII: S0959-8049(00)00406-8

was sufficient to produce therapeutic serum concentrations in most patients. Thus, in early phase II trials, a weekly trastuzumab dose of 100 mg was used, with a 250-mg initial dose being used to achieve therapeutic serum concentrations rapidly. Side-effects were generally mild to moderate in severity; most typically, fever and chills were noted with the first dose [14,15]. The development of neutralising antibodies observed with muMAb 4D5 occurred in only one patient treated with trastuzumab. These results, together with the tumour responses also observed in these studies, justified progression to larger phase II and subsequently to pivotal clinical trials of trastuzumab.

The pivotal trials examined the safety and efficacy of trastuzumab both alone and in combination with chemotherapy. For these trials, the concept of adjusting dose based on body weight was introduced, with an initial dose of 4 mg/kg and subsequent weekly doses of 2 mg/kg being selected based on pharmacokinetic data. When used as a single agent in heavily pretreated HER2-positive patients, trastuzumab produced response rates of 15–20% [16]. The response rate appeared to be independent of any previous chemotherapy for advanced disease. Combining trastuzumab with cytotoxic chemotherapy, such as paclitaxel, enhanced the response rate and improved progression-free and overall survival when given as first-line treatment [17,18].

The importance of the patient's HER2 status in metastatic disease has led to the incorporation of this factor in the breast cancer treatment algorithm. However, questions regarding which method of testing for HER2 is most accurate and reliable and appropriate cut-off levels for determining HER2 status remain. Nevertheless, the introduction of selective agents directed at novel therapeutic targets, such as trastuzumab, may improve outcome in certain patient groups. This supplement reviews the value of HER2 as a prognostic and predictive marker, techniques used to test patients' HER2 status, and clinical trial experience with this exciting new addition to the breast cancer treatment algorithm.

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