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The effects of HER2 monoclonal antibody in women with HER2-overexpressing metastatic breast cancer

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HER-2, metastatic breast cancer, monoclonal antibody

Introduction

HER2 (also referred to as neu or c-erbB-2) is a gene encoding a transmembrane glycoprotein receptor which is a member of the epidermal growth factor receptor family. Overexpression of the HER2 protein occurs in 25% to 30% of human breast cancers and is associated with a poor prognosis in both node-positive and node-negative patients. It appears that the overexpressed protein has a direct role in increasing the aggressiveness of the tumour cells. Following the identification of the specific HER2 receptor, anti-HER2 antibodies were developed, which in animal models inhibited the growth of overexpressing cells. A recombinant humanized anti-HER2 monoclonal antibody has been subsequently developed which in phase II trials has demonstrated safety and clinical activity in women with overexpressing metastatic breast cancer.

Aims

To evaluate the safety and the efficacy of recombinant humanized anti-HER2 monoclonal antibody administered as a single agent to women with metastatic breast disease.

Comments

This important study demonstrates the clinical efficacy and safety of targeted anti-cancer treatment. For the past 15 or so years a large amount of oncology research has focused on the development of strategies that target the unique aspects of tumour cells so that treatments can be more effective and less toxic. Unfortunately, this large body of research has yet to translate into a significant number of new clinically useful treatments. Recombinant humanized anti-HER2 monoclonal antibody is one such treatment and its activity as a single agent in such a poor prognosis group, with its limited toxicity, is certainly an exciting development. Further information about the clinical benefit of the anti-HER2 antibody will come when the results of the large randomized trial comparing chemotherapy alone to chemotherapy with antibody in metastatic breast cancer patients are published.

Methods

Women eligible for study were those with HER2-overexpressing metastatic breast cancer that had progressed after one or two chemotherapy regimens. Patients with untreated brain metastases or bone-only disease were excluded. Tumour tissue (either the primary or collected from a metastatic site) had to demonstrate HER2 overexpression, which was defined immunohistochemically. Two different antibodies were used and expression scored as 0-3. Patients required a tumour staining sore of either 2 or 3 by either antibody to be eligible. A total of 222 women were enrolled. Patients received a loading dose of antibody at a dose of 4 mg/kg intravenously, followed by a 2 mg/kg maintenance dose at weekly intervals. At disease progression, antibody could be continued, increased to 4 mg/kg/week, or discontinued. Other anticancer treatment was then also allowed. Tumour responses were measured at defined time points and were measured by an independent committee. Safety, adverse effects, quality of life and pharmacokinetic analysis were also evaluated.

Results

A total of 213 patients received at least one dose of antibody. A median of 12 infusions was given (range 1-96). Baseline patient characteristics show that the patients generally had poor prognosis disease, with most having multiple metastatic sites (78%) and visceral disease (72%). Patients were heavily pretreated and 26% had had high dose therapy. A blinded, independent response evaluation committee identified an objective response rate of 15% in the intent-to-treat population. The actual investigators found a 22% objective response rate. In responding patients, the median duration of response was 9.1 months and their time to treatment failure was 11 months (median). This compared to a result of 5.4 months seen using their previous chemotherapy regimen. Including all patients, the median time to disease progression was 3.1 months and the median duration of survival was 13 months. Effects of the antibody were seen in all patient subgroups. In a multivariate analysis, increased time to progression was associated with three factors: a single site of metastatic disease, HER2 overexpression at the 3+ level, and less than 6 months to first relapse. Pharmacokinetic analysis showed an elimination half-life of 6.2 days.

Discussion

Recombinant humanized anti-HER2 monoclonal antibody, administered as a single agent, is safe and is active. In a population of heavily pretreated women with progressing poor-prognosis metastatic breast cancer it produces durable objective responses and is well tolerated. The 15% response rate (22% as judged by the direct investigators) and the median duration of response and survival compare favourably with other agents used in this setting such as single agent docetaxel and vinorelbine. An advantage to the antibody is that the side effects commonly seen with chemotherapy, such as alopecia, mucositis, and

neutropenia, are rarely seen, although cardiac toxicity was noted. In conclusion, recombinant humanized anti-HER2 monoclonal antibody is a new treatment option for women with progressive metastatic tissue which overexpresses HER2.

Additional information

Most patients (84%) had at least one adverse effect possibly related to antibody treatment. However only 14% of these were recorded as serious. The most common events were mild/moderate infusion-associated chills/fever that mainly occurred only during the first infusion, and were treated successfully. The most clinically significant adverse event was cardiac dysfunction, which occurred in 10 (4.7%) patients. Of these 10 patients, 9 had received anthracyclines and had a risk factor for anthracycline-induced cardiomyopathy, and the other had significant cardiac disease at study entry. Only one patient had detectable levels of antibodies against the HER2 humanized antibody.

References

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