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An immunotherapeutic approach to treatment of breast cancer: focus on trastuzumab plus paclitaxel

Abstract Recent emphasis has focused on the development of an immunotherapeutic approach toward the treatment of breast cancer. In particular, evaluation of antibodies and vaccines are active areas of research. The monoclonal antibody trastuzumab (H), directed against the HER-2/neu protein, has resulted in inhibition of tumor growth in both preclinical and clinical studies. This effect can be increased when used in combination with several chemotherapeutic agents. A randomized trial of chemotherapy alone versus chemotherapy plus H in untreated metastatic breast cancer patients found prolonged survival in the combination therapy arm. Cardiac toxicity was increased with doxorubicin and cyclophosphamide plus H but not for paclitaxel (T) plus H. Several trials of dose-dense weekly T have found minimal toxicity and significant clinical benefit. These findings prompted the initiation of a trial to evaluate weekly 1-h T plus weekly H. Preliminary data from this ongoing study demonstrate few side effects and a response rate of 64% (95%CI 42–76%). The optimal role of H in the treatment of breast cancer has not yet been defined. Additional evaluation in the metastatic and adjuvant settings is planned.

Key words Immunotherapy · Breast cancer · Trastuzumab · Paclitaxel

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Introduction

Although chemotherapy and hormone therapy are the most common modes of systemic therapy for breast cancer, an immunotherapeutic approach to treatment has shown promising results. Investigation of the optimal role of antibodies and vaccines [5, 7] in the treatment of both early and advanced-stage breast cancer is ongoing. Thus far, the most clinically effective antibody is directed against the HER-2/neu protein.

The HER-2/neu protein is a 185-kD transmembrane protein encoded by the HER-2/neu gene and is homologous to the epidermal growth factor receptor [20]. Overexpression of HER-2/neu, usually in association with gene amplification, occurs in approximately 25–30% of breast cancers [20]. Several studies have demonstrated a less favorable outcome for HER-2/neu-overexpressing breast tumors [18, 19]. More recent evidence has identified HER-2/neu expression as a possible predictive factor for determining response to chemotherapeutic agents [1, 11, 12, 22].

Preclinical studies have reported inhibition of tumor growth in breast cancer cells in vitro and in breast cancer xenografts following administration of the murine monoclonal antibody 4D5 [8, 9]. This antibody, which binds to the extracellular domain of HER-2/neu, has been humanized, leading to production of an IgG1 antibody containing murine elements in the complementarity-determining regions [3]. Subsequent preclinical evaluation of this recombinant antibody, rhuMAb HER-2 (trastuzumab, H [Herceptin]), showed an antiproliferative effect in breast cancer xenografts which may increase when it is used in combination with various chemotherapeutic agents [14, 16]. Mechanisms of action of this antibody may involve disruption of DNA repair [16] and induction of antibody-dependent cellular cytotoxicity [3].

Clinical trials of trastuzumab

Following initial phase I trials, several phase II clinical trials were conducted in metastatic breast cancer patients. A study by Baselga et al. [2] evaluated 46 patients with HER-2/neu overexpressing tumors and measurable disease. The treatment schedule was based on earlier studies [2, 3] that found tumor inhibition at trough serum levels of 10 mcg/mL of antibody. rhu-MAb HER-2 was administered at a loading dose of 250 mg iv over 90 min on day 0, followed by weekly doses of 100 mg iv × 10 weeks. Patients could continue on therapy until disease progression.

Approximately 83% of patients had received ≥1 chemotherapy regimen for metastatic disease. Few toxicities, including transient fever and chills, were noted. The overall response rate was 11.6% (95% confidence interval [CI] 4.36–25.9) in 43 evaluable patients. No human anti-human antibodies were detected; the mean serum $t_{1/2}$ of rhu-NMb HER-2 was 8.3 ± 5.0 days.

In another phase II trial [13], 39 patients with metastatic breast cancer were administered the same schedule of rhu-MAb HER-2 but with the addition of cisplatin 75 mg/m^2 on days 1, 29, and 57 with a maintenance dose until disease progression. Approximately 90% of patients had received ≥2 prior chemotherapy regimens for metastatic disease. Toxicities primarily consisted of those expected with cisplatin alone, including asthenia, gastrointestinal symptoms, and low blood counts. A 24.3% overall response rate (all partial responses) was achieved in 37 evaluable patients, with a median response duration of 5.3 months. No antibodies were detected against rhu-MAb HER-2 in the 748 doses administered.

A subsequent trial of H evaluated 222 patients with HER-2-overexpressing metastatic breast cancer [4]. All patients had received prior chemotherapy for metastases; 32% had received one regimen and 68% two regimens. After a median follow-up of 12.8 months, the overall response rate (complete and partial remission) was 21% (95%CI 16–27%). A 15% (95%CI 11–21%) response rate was reported by an independent response committee, with a median response duration of 9.1 months. There was minimal toxicity, although cardiac toxicity was reported in nine patients.

To evaluate further the combination of chemotherapy and H, a randomized trial was conducted in patients with untreated metastatic breast cancer [21]. Four hundred and sixty-nine patients with HER-2/neu-overexpressing tumors were enrolled; 234 received chemotherapy alone and 235 received chemotherapy plus H. Chemotherapeutic agents included doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 iv (AC), or T 175 mg/m^2 over 3 h iv; both regimens were given every 3 weeks × six cycles. Patients treated with adjuvant doxorubicin received T. H was administered at a loading dose of 4 mg/kg followed by 2 mg/kg/week iv. After a median follow-up of 10.5 months, the response rates were: chemotherapy alone 36.2%; chemotherapy plus H 62%; AC 42%; AC plus H 64.9%; T 25%; and T plus H 57.3%. The time to disease progression was also prolonged for the chemotherapy plus H group. Grade 3–4 cardiac toxicity was more frequent in the AC plus H group (18%) versus the AC (3%), T (0%), or T plus H (2%) groups.

This trial was updated by Norton et al. in 1999 [10]. The median overall survival was superior for the chemotherapy plus H arm versus chemotherapy alone (25.4 versus 20.9 months, $P = 0.045$) at a median follow-up of 25 months (range 20–41 months). These findings were consistent in the subgroups of AC plus H versus AC (33.4 versus 24.5 months), and T plus H versus T (22.1 versus 18.4 months). Upon disease progression, many patients received H in addition to other chemotherapy regimens. Despite the subsequent or continued administration of H, the overall survival was greater in patients who had received the initial combination of chemotherapy plus H. The increased incidence of grade 3–4 cardiac toxicity was again observed to be higher in the AC plus H group (19%) than in the T plus H group (4%).

The findings of these trials led the United States Food and Drug Administration to approve H for the treatment of metastatic breast cancer in patients with HER-2-overexpressing tumors. Specifically, H alone was approved for patients treated with ≥1 prior chemotherapy regimens for metastatic disease and H in combination with T for previously untreated metastatic disease.

Clinical trials of weekly T

Recent data suggest that weekly T infusions are effective therapy for breast cancer. For example, at the Memorial Sloan-Kettering Cancer Center, Seidman and colleagues [17] initiated a trial to evaluate the toxicity and clinical efficacy of weekly T administered as a 1-h infusion in metastatic breast cancer patients. Eligibility criteria included one or two prior chemotherapy regimens, bidimensionally measurable disease, and Karnofsky performance status ≥60%. The initial treatment included T 100 mg/m^2 iv over 60 min with premedication with dexamethasone 20 mg po the night before and morning of treatment, diphenhydramine hydrochloride 50 mg iv, and cimetidine 300 mg iv 30–60 min prior to T. Initially a dose-escalation scheme was planned, but five of nine patients developed grade 3 neuropathy with T doses >100 mg/m^2, and therefore no further dose escalations were carried out. Dose reductions were recommended for grade 3 nonhematologic toxicity, platelet nadirs ≤50,000/mm^3, and infection.

Of the 30 patients treated, all were evaluable for response and 29 were evaluable for toxicity. Twelve of 18 patients treated with prior anthracyclines were identified as anthracycline resistant. The overall response rate was 53% (95%CI 34–72%) with three complete responses and 16 partial responses, with a median response

duration of 7.5 months (range 2–11 + months). There was a 50% response rate among the anthracycline-resistant patients. A median delivered-dose intensity of 91 mg/m^2/week (range 80–108 mg/m^2/week) was observed with a median delivered infusion number of 14 per patient (range 1–44 +).

Grade 3 or 4 myelosuppression was uncommon and there was no evidence of cumulative neutropenia. Grade 1–2 neurotoxicity was observed in 35% of patients but improved in several patients with dose reductions. Two hypersensitivity reactions were observed (one grade 1 and one grade 2), which resolved with diphenhydramine administration and temporary discontinuation of T. In general, the weekly 1-h regimen was well tolerated.

Perez et al. also reported preliminary data from a phase II trial of weekly T infusions in 187 patients with metastatic breast cancer [15]. Prior taxanes were allowed with ≤2 prior chemotherapy regimens for metastatic disease. T 80 mg/m^2 iv was administered as a 1-h infusion. The mean delivered dose was 77.5 mg/m^2/week. In 130 patients, six complete responses and 21 partial responses have been observed. Grade 3–4 myelosuppression without infection occurred in 22 patients. Grade 1–2 neuropathy occurred in 58 patients and grade 3 in 10 patients. This trial also supports the tolerability of a weekly 1-h infusion schedule.

A current Cancer and Leukemia Group B (CALGB) study randomizes patients with metastatic breast cancer to either a T infusion weekly or every 3 weeks to compare clinical efficacy.

Clinical trials of weekly T plus H

Since weekly 1-h T infusions are well tolerated and H plus T every 3 weeks is an effective treatment for metastatic breast cancer, a trial was initiated in 1998 at the Memorial Sloan-Kettering Cancer Center to evaluate a weekly schedule of both agents. Eligibility criteria include bidimensionally measurable disease, ≤3 prior chemotherapy regimens as metastatic or adjuvant therapy, prior taxanes ≥1 year previously, no central nervous system or lymphangitic pulmonary disease, and no prior monoclonal antibody therapy. Immunohistochemical evaluation of HER-2/neu status is required, although patients with HER-2/neu-nonoverexpressing or -overexpressing tumors are eligible for the study.

The treatment schedule includes H 4 mg/kg iv over 90 min on day 0, followed by weekly doses of 2 mg/kg over 30 min beginning on day 7. T administration begins on day 1, followed by weekly doses of 90 mg/m^2 iv over 60 min beginning on day 7. Premedication for T includes dexamethasone 10 mg iv, diphenhydramine 50 mg iv, and cimetidine 300 mg iv 30–60 min prior to T. Patients tolerating the therapy may receive reduced doses of dexamethasone. To monitor for possible cardiac toxicity, multiple-gated acquisition (MUGA) scans or echocardiograms are obtained intermittently (i.e., weeks 8, 16, 28, 40, and 52).

An interim analysis of this ongoing study reported results in 42 patients following 607 infusions [6]. The median number of infusions per patient was 16 (range 1–25) with a median delivered-dose intensity of 82 mg/m^2/week (range 57–90 mg/m^2/week). The median patient age was 50 years (range 33–67 years). Seventy-one percent of patients had received one prior chemotherapy regimen and 17% two regimens. Anthracyclines had been administered to 79% of patients, and taxanes to 17%. The overall response rate was 64% (95%CI 42–76%) in 36 evaluable patients. The response rate in HER-2-positive patients was 71% (95%CI 52–81%), with 20 of 28 patients responding. The response rate in HER-2-negative patients was 37.5% (95%CI 14–66%) with responses in three of eight patients.

Toxicities thus far include grade 3–4 neutropenia (10% of patients and two episodes of febrile neutropenia), grade 2 neuropathy (35%), grade 3 neuropathy (8%), and grade 3–4 diarrhea (7%). There were no significant changes in cardiac function, except in one patient who developed transient congestive heart failure after receiving a total doxorubicin dose of 615 mg/m^2. Results so far suggest that this regimen is well tolerated with minimal toxicity.

As this trial is ongoing and the data are preliminary, no definitive conclusions can be made regarding differences in response rates for HER-2-overexpressing or -nonoverexpressing tumors. The current CALGB trial comparing 1-h infusion of T weekly versus every 3 weeks has been revised to include H.

Conclusions

H has demonstrated significant clinical benefit in patients with breast cancer, although its optimal role remains undefined. Other areas of active investigation include evaluation of the combination of H with other chemotherapeutic agents, such as liposomal doxorubicin, gemcitabine, docetaxel, carboplatin, and T. Other trials will incorporate H in the adjuvant setting in addition to combinations with hormonal therapy. The development of an immunotherapeutic approach to the treatment of breast cancer remains a promising area of research.

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