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Controversies Regarding the Optimal Dose of Nab-Paclitaxel Combined With Gemcitabine in a Phase 1 Trial of Patients with Metastatic Breast Cancer

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Abstract

Nano-particle albumin-bound paclitaxel (nab-paclitaxel) has shown significantly higher response rates and time to progression than has solvent-based paclitaxel in patients with metastatic breast cancer. The potential advantages of nab-paclitaxel led us to investigate the combination of nab-paclitaxel and gemcitabine instead of already proven combination regimens of paclitaxel with gemcitabine. Therefore, an open-label, multicenter, phase I trial was conducted to determine the maximum tolerated dose (MTD) and recommended dose (RD) of combination therapy with nab-paclitaxel and gemcitabine in patients with metastatic or recurrent breast cancer. Nab-paclitaxel was administered intravenously on day 1, and gemcitabine was administered intravenously on days 1 and 8 of a 21-day cycle. Nab-paclitaxel was administered at a starting dose of 220 mg/m2 (Level 1) and escalated to 260 mg/m2 (Levels 2-3), and gemcitabine was administered at a starting dose of 1,000 mg/m2 (Levels 1-2) and escalated to 1,250 mg/m2 (Level 3) by using a traditional 3 + 3 dose-escalation scheme in cohorts of three patients. Three patients were treated in Level 1 and no dose-limiting toxicities (DLT) occurred. In Level 2, additional patients were needed because one DLT was observed in 3 cohort patients. This study was ultimately terminated before defining the RD for two reasons: slow accrual and the results of a similar phase I study were reported by another study group. However, the result was different from ours. Although our study could not determine the MTD and RD, it illustrates that novel approaches should be considered to improve the efficiency of clinical studies.

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Introduction

Breast cancer is the most frequent malignancy in women, with an estimated 89,400 new diagnoses in 2015. The disease is the fifth leading cause of cancer deaths in women, and an estimated 13,800 women in Japan died in 2015 [1]. Although often curable when localized to the breast and local lymph nodes, if the disease becomes metastatic, it is usually not curable. Therefore, treatment objectives for metastatic breast cancer (MBC) are to prolong survival and improve quality of life [2].

Chemotherapies for patients with MBC have undergone remarkable development in recent years; however, conventional anthracycline and taxane-containing regimens continue to be important in this treatment. For cases of human epidermal growth factor receptor type 2 (HER2)-negative breast cancer, the treatment options are limited relative to those for HER2-positive cases and development of highly efficacious therapy is needed.

It is thought that combining taxanes with other agents may enhance treatment efficacy and produce more favorable safety profiles. Gemcitabine is a pyrimidine nucleotide antimetabolite that is phosphorylated intracellularly to active triphosphate, which inhibits DNA replication and RNA

synthesis. Gemcitabine and paclitaxel are two agents with unique mechanisms of action, non-cross-resistance, and the potential for synergistic antitumor activity. Given these mechanisms, gemcitabine and paclitaxel (GT) combination chemotherapy was examined. A phase III study of GT combination chemotherapy demonstrated superior antitumor activity in anthracycline-pretreated patients with MBC who showed an overall survival (OS) of 18.6 months; by comparison, the OS for paclitaxel alone was 15.8 months [3]. The response rate (RR) was better for GT (RR 41.4%; 7.9% showed complete responses (CR)) than for paclitaxel alone (RR 26.2%; 4.6% showed CR).

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is a solvent-free formulation in which paclitaxel is delivered as a suspension of albumin nanoparticles (average size, 130 nm), which eliminates the need for premedication or special infusion sets and allows an infusion to be safely given over 30 min. Additionally, the albumin-bound nanoparticle was designed to preferentially deliver paclitaxel to tumors by biologically interacting with albumin receptors that mediate drug transport [4]. Nab-paclitaxel was compared directly with solvent-based paclitaxel in a randomized phase III trial in 454 women with MBC [5]. In this study, nab-paclitaxel 260 mg/m^2 administered every 3 weeks showed significantly higher response rates and time to progression and a decreased incidence of grade 4 neutropenia relative to those for solvent-based paclitaxel 175 mg/m^2 administered every 3 weeks. The proven efficacy of GT combination and the potential advantages of nab-paclitaxel led us to investigate the combination of nab-paclitaxel and gemcitabine. Therefore, we conducted a phase I trial of nab-paclitaxel in combination with gemcitabine for patients with metastatic or recurrent breast cancer.

Methods

Patient eligibility

Patients who met the following major criteria were considered eligible to participate in the study: women with histologically confirmed breast cancer who were aged 20-75 years; patients with inoperable metastatic or recurrent breast cancer; patients with HER2-negativity demonstrated by immunohistochemical analysis or fluorescence in situ hybridization; patients previously treated with single-regimen or no chemotherapy for MBC; an Eastern Cooperative Oncology Group performance status of 0 or 1; patients for whom each laboratory test value within 14 days before enrollment was within the following ranges: white blood cell count ≥4,000/mm^3, absolute neutrophil count (ANC) ≥ 2,000 /mm^3, hemoglobin concentration ≥9.0 g/dL, platelet count ≥100,000 /mm^3, total bilirubin ≤1.5 mg/dL, serum aspartate aminotransferase (AST) concentration ≤2.5 × the upper limit of normal (ULN), serum alanine aminotransferase (ALT) concentration ≤2.5 × the ULN, and serum creatinine ≤1.5 mg/dL.

However, patients with tumor progression during or within 6 months after the last dose of pre- or postoperative chemotherapy were excluded from the study. Patients with grade ≥1 peripheral neuropathy before enrollment were also excluded. Disease measurable by using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was not required. The study was approved by the Institutional Review Board of all participating institutions, and all patients gave informed written consent before entry into the trial.

Study design

An open-label, multicenter, phase I trial was conducted through the Tokushukai Group to determine the maximum tolerated dose (MTD) and recommended dose (RD) of combination therapy with nab-paclitaxel and gemcitabine in patients with metastatic or recurrent breast cancer. Secondary objectives were to determine the RR, safety, and safe dose for phase II evaluation.

Nab-paclitaxel was administered intravenously over 30 minutes before gemcitabine on day 1, and gemcitabine was administered intravenously over 30 minutes on days 1 and 8 of a 21-day cycle until the occurrence of disease progression or development of intolerable toxicities. Prophylactic antiemetics (including corticosteroids) and growth factors for hematologic toxicity were permitted. Nab-paclitaxel was administered at a starting dose of 220 mg/m^2 (Level 1) and escalated to 260 mg/m^2 (Levels 2-3), and gemcitabine was administered at a starting dose of 1,000 mg/m^2 (Levels 1-2) and escalated to 1,250 mg/m^2 (Level 3) by using a traditional 3 + 3 dose-escalation scheme in cohorts of 3 patients. Three to 6 patients were enrolled at each dose level. Toxicities were graded according to the Common Terminology Criteria for Adverse Events version 4.0. If no dose-limiting toxicity (DLT) was observed for the first 3 patients at a given dose level, escalation proceeded to the next dose level. Initially, only the first cycle was used to determine the DLT. After the first DLT, ≤3 more patients were enrolled at that same dose level. Escalation continued only if DLT was limited to 1 of 6 patients. Escalation halted if DLT occurred in ≥2 patients. When DLT was observed in ≥2 of 6 patients at any level, that level was considered to be an MTD, and the dose level immediately below that level was defined as an RD. There was no interpatient dose escalation.

DLT was defined as grade 4 thrombocytopenia, grade 3 thrombocytopenia requiring platelet transfusion, grade 4 neutropenia lasting for >4 days, grade 3 or 4 febrile neutropenia (FN), a >7-day delay on day 8 caused by an ANC of <1,000/mm^3 or a platelet count of <70,000/mm^3, grade 3 or 4 peripheral neuropathy, grade 3 or 4 non-hematologic toxicity (with the exception of nausea, vomiting, or anorexia), or other adverse events that led to a ≥21-day delay in the start of Cycle 2.

Results

From August 2011 to March 2016, 7 patients were enrolled. The patient characteristics are listed in Table 1. The median age was 64 years (range, 46-72 years), and all patients had histologically negative HER2 status. Most patients had received previous hormonal therapy, and no patient had received any previous chemotherapy for MBC. The dose levels studied are summarized in Table 2. Three patients were treated at Level 1 (nab-paclitaxel 220 mg/m^2, gemcitabine 1,000 mg/m^2) and no DLT occurred. In Level 2 (nab-paclitaxel 260 mg/m^2, gemcitabine 1,000 mg/m^2), additional patients were needed because 1 DLT (grade 3 AST increase) was observed in 3 cohort patients. Then, 1 additional patient was treated without DLT; however, the study was ultimately terminated because of slow accrual. Therefore, the MTD could not be determined in this study.

All 7 subjects were evaluable for adverse events. Table 3 presents the number of adverse events that were determined to be clinically relevant by the investigator at each dose level. The hematological toxicities with high incidence were neutropenia (86%; n = 6), leukopenia (71%; n = 5), and anemia (71%; n = 5). The non-hematological toxicities with high incidence included AST increase (100%; n = 7), ALT increase (86%; n = 6), peripheral neuropathy (86%; n = 6), and alopecia (86%; n = 6). The most commonly reported Grade 3 or 4 toxicity related to therapy was neutropenia.

Three patients were taken off the study because of treatment delay due to neutropenia and required dose reduction in 1 patient. Of the 6 patients who developed peripheral neuropathy, 2 were taken off the study because of continuation of Grade 2 toxicities. The most frequent toxicities were increases in AST/ALT; although most patients were manageable, 1 patient developed DLT.

Of the 7 patients enrolled in the study, 3 patients in Level 1 were evaluable for response by RECIST version 1.1. In Level 2, 1 patient had no measurable lesion, and 3 patients were taken off the study prior to first restaging analysis. The reasons for withdrawal were occurrence of DLT in Cycle 1in 1 patient and delayed treatment due to neutropenia in Cycle 2 in 2 patients. The responses in the 3 patients included partial response in 1 patient and stable disease in 2 patients (Table 2).

Discussion

Combination chemotherapy represents a treatment choice that has been prescribed for increased efficacy. Although the utility of combination chemotherapy or sequential single-agent treatment is controversial [6], patients with MBC who receive combination chemotherapy have improved progression-free and overall survival rates [7-8], and some have long-term remissions [9]. In this way, most patients with MBC treated with systemic therapies have only temporary responses to treatment, but some patients show CR following initial treatment. Greenberg et al. reported that of all patients who achieve CR, approximately 18% remain disease-free for >5 years following treatment with doxorubicin and alkylating-agent-based regimens; >10% remain disease-free for periods >20 years [10]. These data show that a small percentage of patients achieve long-term remissions with standard chemotherapy regimens and a small percentage of patients with MBC can achieve very long-term unmaintained CR with systemic therapy. Therefore, combination chemotherapies as attempts to achieve CR have been expected for use in trials to show improvement in OS. Therefore, this phase I multicenter trial was undertaken to identify the MTD and RD for phase II evaluation of nab-paclitaxel and gemcitabine combination in patients eligible to receive first- or second-line chemotherapy for MBC and to assess the safety and overall RR for this combination in patients with MBC. In a phase III trial, a combination of GT for first-line treatment of anthracycline-pretreated, taxane-naïve, MBC patients was associated with an RR of 41.4% and time to progression (TTP) of 6.14 months [3]. The GT regimen was associated with a longer TTP, an OS advantage, and a manageable toxicity profile relative to those for three times weekly paclitaxel alone. In this trial, FN was reported in 5.0% of patients on GT. In contrast, no FN occurred in the patients who received nab-paclitaxel and gemcitabine combination in our study. However, grade 3 to 4 neutropenia was more commonly observed in our study (86% nab-paclitaxel and gemcitabine, 47.9% GT). The incidences of grade 2 peripheral neuropathy were higher in our study (57% nab-paclitaxel and gemcitabine, 24.5% GT); however, grade 3 to 4 peripheral neuropathy was lower for this treatment in our study than for GT (0% vs. 8.4%). The incidences of increases in grades ≥2 of AST/ALT were also higher in our study.

This study was ultimately terminated before defining the RD for 2 reasons. First, accrual was very slow because this combination chemotherapy with possible toxicities was not attractive for patients. Second, the results of a similar phase I study were reported by another study group [11]. However, Yoshitomi et al. reported that DLTs did not occur in any cohorts and the RD was 1,250 mg/m^2 for gemcitabine and 260 mg/m^2 for nab-paclitaxel; nevertheless, these results differed from those in our study. In this study, dose settings were different from our study; nab-paclitaxel had been started from a lower dose. Furthermore, in a randomized phase II clinical study, the median progression-free survival and RR of weekly nab-paclitaxel was 12.9 months and 49%, respectively, which suggested that weekly nab-paclitaxel might be superior to triweekly administration [12]. In first-in-human clinical trials that include new combination chemotherapies, a dose-escalation study design is often used. The most commonly used dose-escalation study design is the traditional 3 + 3 design, which guides "up-and-down" decisions, using the modified Fibonacci mathematical series to determine the amount of dose increase for cohorts of sequentially enrolled patients. This traditional 3 + 3 design belongs to rule-based methods, which use pre-specified rules based on actual observations of target events as DLT from the clinical data to assign patients to dose levels and determine the MTD or RD for a phase II trial [13]. The principle for dose escalation in phase I trials is to avoid exposing too many patients to subtherapeutic doses while maintaining safety and rapid accrual. The main advantages of the traditional 3 + 3 design are that it is simple to implement, does not require special software, and is safe. In addition, accrual of 3 patients per dose level provides additional information about pharmacokinetic interpatient variability. However, a disadvantage of this design is that it involves an excessive number of escalation steps, which results in a large proportion of patients who are treated at subtherapeutic doses while few patients actually receive doses at or near the RD for phase II trials.

Generally, accrual of patients with MBC to early-phase trials is particularly low, despite data suggest that patients with MBC enrolling in phase I trials may have improved survival outcomes [14]. Poor accrual may be a critical barrier to progress in clinical studies. This phase I study could not determine the MTD and RD, which illustrates that novel approaches are needed to improve the efficiency of clinical studies.

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