Clinical Effect of Irinotecan in Advanced and Metastatic Breast Cancer Patients Previously Treated with Doxorubicin- and Docetaxel-containing Regimens

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Background: Previous phase II trials in Japan suggested that irinotecan was a promising agent for advanced or metastatic breast cancer pretreated with anthracycline. However, irinotecan has not yet been evaluated in the salvage setting for breast cancer pretreated with both anthracycline and taxane, which are two active agents for breast cancer.

Methods: The efficacy and safety of irinotecan were retrospectively evaluated in patients with breast cancer who had previously been treated with both doxorubicin and docetaxel. From 1996 to 1999, irinotecan was administered to 20 patients, all with a performance status of <2. Irinotecan treatment was repeated in ~6 week cycles consisting of the administration of irinotecan once weekly for 4 weeks followed by a 2 week rest. The median dose of irinotecan administered was 100 mg/m2 weekly. The median number of irinotecan cycles given was 1 (range: 1–8 cycles). The median total dose was 388 mg/m2 (range: 50–2400 mg/m2).

Results: Performance status declined to >3 after treatment with irinotecan in four patients. Two patients had grade 3 leukopenia; three had grade 3 anemia and one had a creatinine elevation of grade 4. The objective response rate for all patients was 5.0% (95% CI: 0–15.5%). The median time to progression and overall survival were 35 days (range: 17–285 days) and 124 days (range: 17–667 days), respectively, since the start of the administration of irinotecan.

Conclusions: Salvage chemotherapy with irinotecan may be inactive against advanced and metastatic breast cancer pretreated with doxorubicin and docetaxel. We will evaluate irinotecan for advanced and metastatic breast cancer patients as first- or second-line chemotherapy combined with anthracycline or taxane.

Key words: breast cancer – chemotherapy – irinotecan – salvage treatment – drug resistance

INTRODUCTION

Irinotecan, a water-soluble analog of camptotecin, is an inhibitor of DNA topoisomerase I developed in Japan (1). It has clinical therapeutic efficacy against various malignancies such as cervical, colorectal, lung and ovarian cancers and non-Hodgkin’s lymphoma. Although irinotecan has been reported to be inactive for salvage therapy of breast cancer in Europe (2), it was approved for use in breast cancer in Japan. A series of phase II trials in Japan were undertaken from 1987 to 1993 (3,4). Considering efficacy and safety, 100 mg/m2 weekly was selected as the recommended dose. The objective response rate was reported to be 23% in a late phase II study. The response rates in patients with prior endocrine therapy or prior chemotherapy, including doxorubicin or other anthracyclines, were 27 and 26%, respectively. Major adverse reactions were myelosuppression and gastrointestinal symptoms. These results suggested that irinotecan was a promising drug for advanced or metastatic breast cancer.

Docetaxel, an antimicrotubule agent of the taxane class, has proved useful in treating patients with breast cancer (5). It has a high degree of efficacy not only in patients who have never received chemotherapy, but also in those who failed to respond to chemotherapy, including the anthracyclines (6). As a result, irinotecan is used for salvage chemotherapy for breast cancer pretreated with both doxorubicin and docetaxel. Docetaxel had not been included among the agents used for chemotherapy in the previous phase II trials with irinotecan, because it had not become available for clinical treatment at that time. Therefore, irinotecan has not been sufficiently evaluated in situations in which docetaxel has been part of previous treatment. In this case, irinotecan may be inactive against advanced and metastatic breast cancer.
study, we investigated retrospectively the efficacy and safety of irinotecan against advanced and metastatic breast cancer previously treated with both doxorubicin and docetaxel.

**PATIENTS AND METHODS**

**PATIENTS**

Primary end-points in this analysis were response rate and toxicity. Twenty patients were administered irinotecan from January 1996 to July 1999, after they had been treated with doxorubicin and docetaxel. All patients were histologically confirmed as having breast cancer. When irinotecan was administered, 19 patients had primary advanced or metastatic breast cancer and one patient had only local recurrence of breast cancer.

**TREATMENT SCHEDULE**

After written informed consent had been obtained, irinotecan was administered intravenously as a 90 min drip infusion at a dose of 100 mg/m² weekly, as approved in Japan. As a rule, irinotecan was repeated in ~6 week cycles consisting of the administration of irinotecan once weekly for 4 weeks followed by a 2 week rest. The treatment was repeated until disease progression or apparent severe toxicity was observed. The next course started after the leukocyte count recovered (WBC ≥3000/mm³). Dose and treatment schedule modifications were based on leukopenia, diarrhea or creatinine elevation.

**TREATMENT EVALUATION**

All patients were evaluated by a complete blood cell count and serum chemistry studies before the administration of irinotecan. Performance status according to the Eastern Cooperative Oncology Group was evaluated before and after therapy. Toxicity was graded according to the National Cancer Institute’s clinical trials common toxicity criteria, version 2.0, from the start of administration of irinotecan to the end of the fourth week following the final administration. Response was evaluated during or after the first cycle in all patients. After the first cycle was completed, evaluation of response was performed at least every four cycles according to WHO criteria (7).

Time to progression (TTP) was defined as duration from the starting day of treatment with irinotecan to the day on which a judgment of disease progression was made. Overall survival (OS) was defined as the duration from the starting day of treatment with irinotecan to the day the patient died. The survival curve was calculated according to the Kaplan–Meier method (8). The log-rank test was used to assess the significance of the difference between pairs of survival probabilities (9).

**DEFINITION OF DRUG RESISTANCE**

Drug resistance was defined as follows: progression during or within 3 months of treatment for advanced and metastatic breast cancer or relapse during or within 6 months of adjuvant chemotherapy.

**RESULTS**

Characteristics of the 20 patients are shown in Table 1. All patients had been treated with doxorubicin and docetaxel before the administration of irinotecan. Doxorubicin was administered for advanced or metastatic breast cancer in 17 patients and as adjuvant chemotherapy after surgery for primary breast cancer in four patients. One of these patients was initially administered doxorubicin as adjuvant chemotherapy and was later treated again with doxorubicin for tumor recurrence. Although docetaxel was administered to all patients, it was not used as adjuvant chemotherapy. The median interval between the final day of the previous chemotherapy and the starting day of the administration of irinotecan was 33 days (range: 17–213 days).

Before the administration of irinotecan, 10 patients had resistance to both doxorubicin and docetaxel. Four patients had resistance to docetaxel without resistance to doxorubicin. Five patients did not have resistance to either doxorubicin or docetaxel. One patient had resistance to doxorubicin and docetaxel was discontinued early in the first course because of a hypersensitive reaction. The median number of irinotecan cycles administered was 1 (range: 1–8 cycles). The median total dose of irinotecan was 388 mg/m² (range: 50–2400 mg/m²). The performance status declined to >3 after treatment with irinotecan in four patients.

**TOXICITY**

Toxicities are shown in Table 2. All patients were assessable for toxicity. Two patients had grade 3 neutropenia and three had grade 3 anemia. Non-hematological toxicities were mild. However, a creatinine elevation of grade 4 was observed in one patient. She was administered irinotecan in an outpatient setting and grade 2 diarrhea occurred during the seventh cycle. The serum creatinine level elevated rapidly after diarrhea continued for 5 days. After artificial dialysis was introduced, the creatinine level quickly recovered.

**THERAPEUTIC ACTIVITY**

All patients were assessable for response. Partial response occurred in one patient with neck lymph node metastasis only. She had resistance to doxorubicin, but docetaxel was discontinued because of a hypersensitive reaction early in the first course. Partial response was observed after the administration of three cycles, but irinotecan was discontinued because of a serum creatinine elevation of grade 4.

Seven patients had stable disease and twelve patients had disease progression while on therapy. None with resistance to both doxorubicin and docetaxel responded to irinotecan. The overall response rate was 5.0% (95% CI: 0–15.5%). The median TTP was 35 days (range: 17–285 days) and the median
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OS was 124 days (range: 17–667 days) in all patients (Figs 1 and 2). The median TTP was 35 days (range: 17–185 days) in the 10 patients with resistance to both doxorubicin and docetaxel and 54 days (range: 23–285 days) in the other 10 patients. There was no significant difference in TTP between these two groups ($p = 0.285$). The median OS was 99 days (range: 17–560 days) in the 10 patients with resistance to both doxorubicin and docetaxel and 138 days (range: 48–667 days) in the other 10 patients. There was no significant difference in OS between the two groups ($p = 0.334$). As of May 2000, 17 patients had died by disease progression and three patients remained alive.

DISCUSSION

When a promising new drug appears, the position of conventional drugs in treatment strategy changes. Therefore, anticancer drugs need to be evaluated not only in clinical trials but also after introduction to the market place. Particularly the drugs that are approved in only a few countries and are not used universally must be evaluated in each country. Irinotecan is used internationally in the treatment of colorectal cancer and some large randomized trials have shown it to be the standard agent for second-line chemotherapy after treatment with 5-FU (10, 11). On the other hand, in breast cancer, irinotecan is considered a domestic drug in Japan. Irinotecan has never been evaluated for breast cancer in Japan after completion of phase II trials. Therefore, further evaluation was needed for irinotecan, because it is now possible to use docetaxel clinically.

This retrospective analysis showed that salvage chemotherapy with irinotecan may be inactive against advanced and metastatic breast cancer pretreated with both doxorubicin and docetaxel. The objective response rate was only 5.0% (95% CI: 0–15.5%) and the median time to progression was 35 days.
These results indicated very low activity compared with the result of phase II trials in Japan, in which docetaxel had not been used in previous treatment.

Systemic chemotherapy is widely used for advanced and metastatic breast cancer, but without sufficient survival benefit. Salvage chemotherapy consisting of anticancer drugs other than anthracycline and taxane generally demonstrates poorer response and shorter survival (12). Capecitabine, which is one of the new generations of oral fluoropyrimidines, has recently attracted attention since it allows home-based therapy, but its response rate did not exceed 20% in metastatic breast cancer after failure of paclitaxel and an anthracycline-containing regimen (13). It was reported that the median survival duration after second- or third-line chemotherapy in patients who had received anthracyclines was less than 6 months before the introduction of the taxanes (14). Therefore, although the median overall survival after the administration of irinotecan was 124 days in our analysis, it cannot be concluded that treatment with irinotecan might shorten survival in historical comparison.

Although irinotecan is also used for the treatment of other malignancies such as colon cancer and small cell lung cancer, it is not administered in the salvage setting after anthracycline and taxane. Specifically, in colorectal cancer, irinotecan was effective in patients who failed to respond to first-line chemotherapy with 5-FU (10,11). In small cell lung cancer with extensive disease progression, a randomized phase III trial demonstrated the efficacy of combination treatment with irinotecan and cisplatin as first-line chemotherapy (15). In cervical cancer, irinotecan showed a response rate of 21% in patients mainly treated with a cisplatin-containing regimen (16).

The reason for the poor response to irinotecan is unknown in this analysis. With regard to the mechanism of drug resistance, DNA topoisomerase I inhibitors have a unique drug resistance mechanism, such as quantitative reduction and subcellular distribution of topoisomerase I, which are different from P-glyco-

protein- and multidrug resistance-associated protein-mediated multidrug resistance (17–20). It is unclear whether these unique mechanisms occur in breast cancer refractory to both doxorubicin and docetaxel. In our analysis, time to progression and overall survival for 10 patients with clinically defined drug resistance to both doxorubicin and docetaxel did not show a significant difference compared with the other 10 patients.

The main reason for the poor response to irinotecan might be the type and number of metastatic sites. The 20 patients had a median of three metastatic sites before the start of irinotecan and most had visceral metastasis. There may have been fewer metastatic sites in the phase II trial conducted in Japan than in our analysis. It should be considered that irinotecan is used before metastatic sites spread to many organs. That is to say, irinotecan may as well be applied as first- or second-line chemotherapy combined with anthracycline or taxane.

This weekly schedule of irinotecan, once weekly for 4 weeks followed by a 2 week rest, was not too intensive for heavily treated patients, because adverse reactions to irinotecan were generally mild except for one patient who had acute renal failure. The grade 4 creatinine elevation was induced by prolonged diarrhea and was not the result of a direct effect of irinotecan on renal function. Actually SN-38, which is a metabolite of irinotecan that can cause toxicity, is mainly eliminated by biliary excretion (21). Although the median number of irinotecan cycles administered was only one, the main reason originates in disease progression itself.

CONCLUSION

The results of this analysis suggest that salvage chemotherapy with irinotecan may be ineffective in advanced and metastatic breast cancer pretreated with both doxorubicin and docetaxel. We will evaluate the administration of irinotecan to advanced and metastatic breast cancer patients as first- or second-line chemotherapy combined with anthracycline or taxane. A phase
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References


