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Drug resistance in chemotherapy for breast cancer

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Abstract Recent developments with chemotherapy for breast cancer have improved patient survival. However, there continue to be nonresponders to conventional anticancer agents. Multidrug resistance (MDR) is caused by the expression of P-glycoprotein (P-gp) on the cell membrane. The expression of P-gp is encoded by MDR1 mRNA in tumors and is associated with clinical drug resistance. Since P-gp appears to be involved in both acquired and congenital MDR in human cancers, P-gp could be an important target for improving the efficacy of chemotherapy. Recently, we have focused on a therapeutic approach to reduce drug resistance in chemotherapy for breast cancer. Dofequidar fumarate (Dof) is a novel, orally active quinoline derivative that reverses multidrug resistance. In preclinical studies, the inhibition of doxorubicin-resistant cancer cell lines was observed in the presence of Dof + doxorubicin. We conducted clinical trials including Dof + cyclophosphamide (C), doxorubicin (A), and fluorouracil therapy (F) for patients with advanced or recurrent breast cancer. We compared the efficacy and tolerability of Dof + CAF with CAF alone. In this randomized, placebo-controlled trial, all patients were treated with six cycles of CAF therapy. Patients received Dof (900 mg p.o.) 30 min before doxorubicin. The primary endpoint was overall response rate (partial or complete response). In total, 221 patients were evaluable. The overall response rate was 42.6% for CAF alone versus 53.1% for Dof + CAF. Although the response rate improved by more than 10% with the combination of Dof + CAF, it was not statistically significant. Initially, we were expecting more than 20% improvement in the overall response rate. However, Dof significantly improved progression-free survival in patients who were premenopausal ($P = 0.046$), who had received no prior therapy ($P < 0.01$), or patients with advanced (stage IV) primary tumors ($P = 0.017$). In addition, treatment with Dof did not affect the plasma concentration of doxorubicin in patients. These clinical studies indicate that Dof was well tolerated and displayed promising efficacy in patients who had not received prior therapy. The antiestrogens, tamoxifen, and toremifene, may moderate P-gp-related drug resistance in vitro. Toremifene demonstrated a synergistic effect in combination with paclitaxel on various human breast cancer cell lines. Furthermore, a synergistic effect was observed on a multidrug-resistant cell line. This synergistic effect was more potent when paclitaxel was combined with toremifene than with tamoxifen. Clinical benefits in some patients with recurrent breast cancer were reported.

Keywords Breast cancer · Chemotherapy · Drug resistance · MDR inhibitor · Toremifene · Paclitaxel

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Introduction

Chemotherapy plays an important role in the treatment of breast cancer and a meta-analysis of Early Breast Cancer Trialists' Collaborative Group data showed a

24% decrease in the annual odds of recurrence, and approximately 15% decrease in deaths [3, 9]. In the past decade, chemotherapy has been associated with improved survival in breast cancer patients, and the mortality rate in North America and the United Kingdom has decreased recently [15, 23]. However, resistance to chemotherapy is a critical issue in the management of patients. There are many clinical data to demonstrate the usefulness of taxane-containing treatment in chemotherapy for breast cancer [31]. The CALGB9344 study [13] as well as the NSABPB-28 trial [21] demonstrated the additional effect of paclitaxel. In the BCIRG 001 study, TAC (docetaxel + doxorubicin + cyclophosphamide) treatment demonstrated statistically significant superior disease-free survival to CAF (cyclophosphamide + doxorubicin + fluorouracil) for primary breast cancer [24]. However, even with the development of new drugs and treatment methods, resistant mechanisms remain. Therefore, consideration must be given to overcoming drug resistance in chemotherapy. The multidrug resistance gene 1 (MDR1) encodes P-glycoprotein (P-gp) on the cell membrane [2]. In addition, P-gp appears to be involved in both acquired and congenital MDR in human cancers [16]. There are some substrates that can bind to P-gp, and these may inhibit the function of P-gp [35]. P-gp substrates that have been reported include verapamil, quinolines, benzothiazepines, and steroids [7]. Dofequidar fumarate (MS 209, Nihon Shering K.K, Tokyo, Japan) is a novel, orally active quinoline derivative that reverses multidrug resistance [1, 29, 32]. Dofequidar has been demonstrated to have an additional effect with doxorubicin-containing regimens in preclinical and clinical studies. In addition, the antiestrogens tamoxifen and toremifene may moderate P-gp-related drug resistance in vitro [8]. Toremifene in combination with paclitaxel demonstrated a synergistic effect on various human breast cancer cell lines. Furthermore, a synergistic effect was observed in a multidrug resistant cell line. In this paper, we summarize the most recent preclinical and clinical data of dofequidar and the rationale for toremifene and paclitaxel combination chemoendocrine therapy for breast cancer.

P-gp expression in breast cancer

P-gp and MRP1 belong to a large family of proteins called the ABC (ATP binding cassette transporters) protein superfamily [8]. P-gp expression in untreated breast cancer has been reported. Approximately 40–50% of primary breast cancers express P-gp according to immunohistochemistry studies [19]. In addition, larger tumors (>2 cm) are more likely to express P-gp than smaller ones. A correlation between P-gp expression and clinical factors has also been reported [33, 34]. After chemotherapy, the incidence of P-gp increases from 40–50% to 60–70% in breast cancer [5, 36].

Dofequidar fumarate

Dofequidar has a chemical structure based on quinoline and directly modulates the function of P-gp; it inhibits the efflux of anticancer drugs. The main metabolites are excreted into urine (data not shown).

Inhibitory effect of the efflux of doxorubicin by dofequidar (in vitro study)

Efflux of ^{14}C-doxorubicin

K562/ADM cells, which demonstrate acquired resistance to doxorubicin, were incubated in a primary medium containing ^{14}C-doxorubicin 50 μM, concurrently with dofequidar 3 μM or 5% verapamil which were added to the medium for 2 h. Subsequently, the conditioned medium was removed and the cells were incubated with medium containing dofequidar, verapamil, or control medium alone as a secondary culture. Dofequidar strongly inhibited the efflux of ^{14}C-doxorubicin from K562/ADM cells. Conversely, without dofequidar, this inhibition was not observed (Fig. 1).

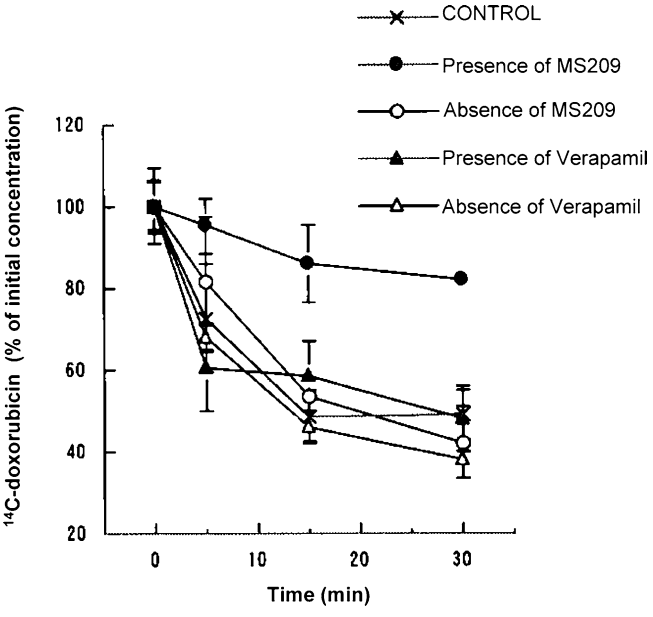

Fig. 1 Efflux of ^{14}C-doxorubicin in the presence of MDR inhibitors. The doxorubicin-resistant cell line K562/ADM was incubated with the first culture medium. Subsequently, the medium was washed from each dish, and a second medium (conditioned medium) was added to each dish. Control: conventional culture medium, i.e., no change of medium (*X*); presence (*closed circle*) or absence (*open circle*) of MS209, conventional medium followed by conditioned medium with or without Dofequidar (MS 209); presence (*closed triangle*) or absence (*open triangle*) of Verapamil, conventional medium followed by conditioned medium with or without 5% verapamil

Specificity of dofequidar

K562 cells, a parental cell line, and K562/ADM cells were incubated with ^{3}H-azidopine for several hours [4, 28]. ^{3}H-azidopine is a ligand for P-gp. Subsequently, dofequidar was added to the conditioned medium. We analyzed the specific band of 170 kDa by Western blotting. In the presence of dofequidar, the expression of P-gp was inhibited in a dose-dependent manner (Fig. 2).

Inhibitory effect on the efflux of doxorubicin by dofequidar (in vivo study)

P388/ADM resistance cell-bearing mice received dofequidar 300 mg for 5 days orally. Concurrently, doxorubicin 2 mg/kg was given intraperitoneally for 5 days. Survival was 194 days in the dofequidar-treated group, but 124 days in the control group, suggesting that dofequidar improved survival in P388/ADM-bearing mice treated with doxorubicin in vivo (data not shown).

Summary of clinical studies

A Phase I clinical study was conducted in Japan. Forty-six healthy volunteers were enrolled and the study was double-blinded. Dofequidar at a dose range from 10 to 1,200 mg was administered once a day (data not shown). The area under the curve (AUC) of non-metabolic compounds increased in a dose-dependent manner (data not shown). An effective plasma concentration (≥3 μM) was maintained for 8 h with dofequidar 900 mg/day. Most adverse events were mild (grade 1–2). At a dose of 1,200 mg/day, one patient complained of grade 3 headaches, but this resolved rapidly. Headache may be related to dofequidar. Other adverse events included fatigue, hot flashes and stomachache. No dose-limiting toxicities were determined. We concluded that dofequidar was well-tolerated at a dose range of 10–1200 mg/day.

An early Phase II study of dofequidar in combination with CAF regimen

To determine drug–drug interactions and a recommended dose of dofequidar in combination with standard chemotherapeutic regimens, we conducted a combination phase I study of dofequidar and CAF. The target population was nonresponder patients with breast cancer who had received a standard CAF regimen [14]. We chose four doses of dofequidar from 300 to 1,200 mg/day based on data from a phase I study. The CAF regimen was fixed: on days 1 and 8, doxorubicin 30 mg/m^2 and fluorouracil 500 mg/m^2 and on days 1–14, cyclophosphamide 100 mg; dofequidar was administered 30 min prior to doxorubicin. We observed an enhancement of antitumor effects with CAF + dofequidar 900 mg/day. Two of six patients responded to CAF + dofequidar 900 mg in this trial. No severe adverse events were reported among 22 patients. It was concluded that the recommended dose for Phase III studies of dofequidar is 900 mg in combination with CAF (W. Sato, personal communication 1998).

A phase III study

To compare the efficacy and safety of dofequidar + CAF versus placebo, we planned a phase III trial in metastatic breast cancer [27]. A total of 238 patients with advanced or recurrent breast cancer were enrolled across 46 centers in Japan. The treatment schedule was 6 cycles of CAF (28 days each), days 1 and 8 doxorubicin

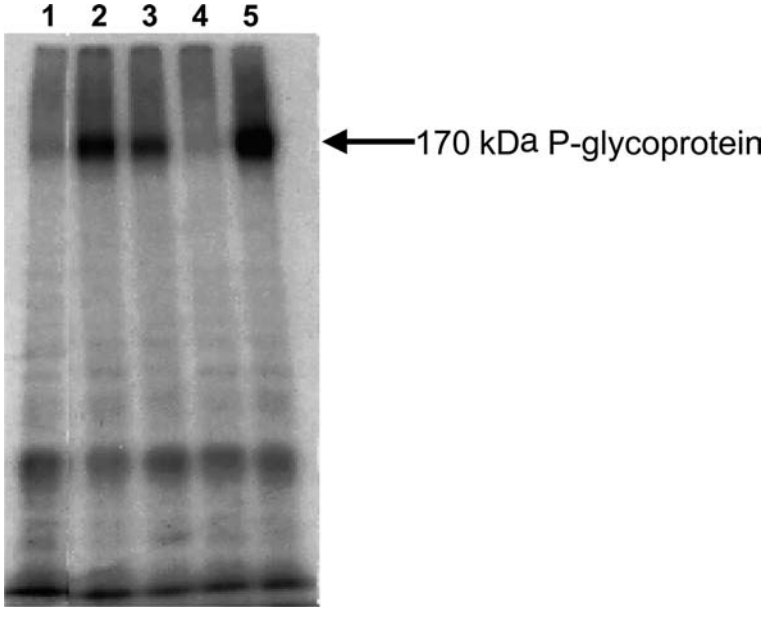

Fig. 2 Binding to P-glycoprotein (P-gp) in K562/ADM cell lines. The 170 kDa protein demonstrated the expression of P-gp in vitro. A doxorubicin-resistant cell line (K562/ADM) expressed P-gp highly in *lane 5* by Western blotting. A parental cell line (K562) did not express the 170 kDa P-gp specific protein in *lane 1*. In the presence of dofequidar, the expression of P-gp was decreased in a dose-dependent manner (*lanes 2–4*) *Lane 1*: parental cell line (K562); *lane 2*: Dofequidar 1 μM; *lane 3*: Dofequidar 10 μM; *lane 4*: Dofequidar 100 μM; *lane 5*: Doxorubicin-resistant cell line (K562/ADM)

(25 mg/m^2) and fluorouracil (500 mg/m^2), days 1–14, cyclophosphamide 100 mg, dofequidar 900 mg/day (3×300 mg tablets) administered 30 min prior to doxorubicin. The primary endpoint was overall response rate (complete response + partial response). The secondary endpoints were progression-free survival (PFS), time to progression (TTP), and time to treatment failure (TTF). In the CAF + dofequidar group, 60 of 113 patients responded (overall response rate 53.1%), and in the CAF + placebo group, the overall response rate was 42.6%. Although there was a 10.5% higher response rate with CAF + dofequidar, it was not statistically significant. However, dofequidar significantly improved PFS in premenopausal patients ($n = 50$; $P = 0.046$), patients who had received no prior therapy ($n = 46$; $P < 0.01$), and patients with advanced (stage IV) primary tumors ($n = 60$; $P = 0.017$). No statistically significant excess of grade 3/4 adverse events was observed in either group. However, dofequidar was associated with an increased incidence of neutropenia and leucopoenia, but there was no significant difference in the incidence of febrile neutropenia between the two groups. We concluded that dofequidar was well tolerated in the clinical setting. In particular, dofequidar displayed promising efficacy in patients who had not received prior therapy. This efficacy was also observed in premenopausal patients and patients with advanced primary tumors.

Antiestrogens may be candidates as a ligand to P-gp in breast cancer

Antiestrogens are used as standard endocrine agents for breast cancer [10, 11]. Antiestrogens such as tamoxifen and toremifene can bind to estrogen receptors and block the signaling pathway to the nuclear receptor [25, 26]. This main mechanism is well known and antiestrogens have proved to be of clinically benefit. In addition, antiestrogens may moderate the function of P-gp and could be candidates as P-gp (MDR) inhibitors [17, 21, 30]. Increased concentrations of doxorubicin in doxorubicin-resistant cells treated with toremifene were evaluated [18]. In controls, the concentration of doxorubicin was low and stable for 2 h. In the presence of toremifene, doxorubicin efflux was inhibited in a time-dependent manner. In the MCF-7/K parental cell line, the concentration of doxorubicin increased in a time-dependent manner in the absence or presence of toremifene in vitro (Fig. 3). In addition, the concentration of ^{14}C-doxorubicin was not affected by a metabolite of toremifene (TOR-1). On the other hand, we treated doxorubicin-resistant cells (Adr^R) with either the same dose of doxorubicin (control) or doxorubicin + toremifene 10 μM. Neither toremifene nor TOR-1 decreased the concentration of ^{14}C-doxorubicin.

Given that CYP3A4 is the main metabolism enzyme for both paclitaxel and toremifene, there may be a drug–drug interaction between the two agents. Paclitaxel is a standard chemotherapeutic agent for breast cancer, and it has demonstrated clinical efficacy against doxorubicin-resistant breast cancer [12]. In addition, P-gp may play an important role in paclitaxel efflux in vitro [6]. We studied combination treatment with toremifene and paclitaxel. To clarify the synergistic effect of paclitaxel and toremifene, we treated doxorubicin-resistant MCF-7 cells with paclitaxel 5 μM and toremifene 10 μM. There might be a synergistic effect of either toremifene or tamoxifen in combination with paclitaxel at a dose

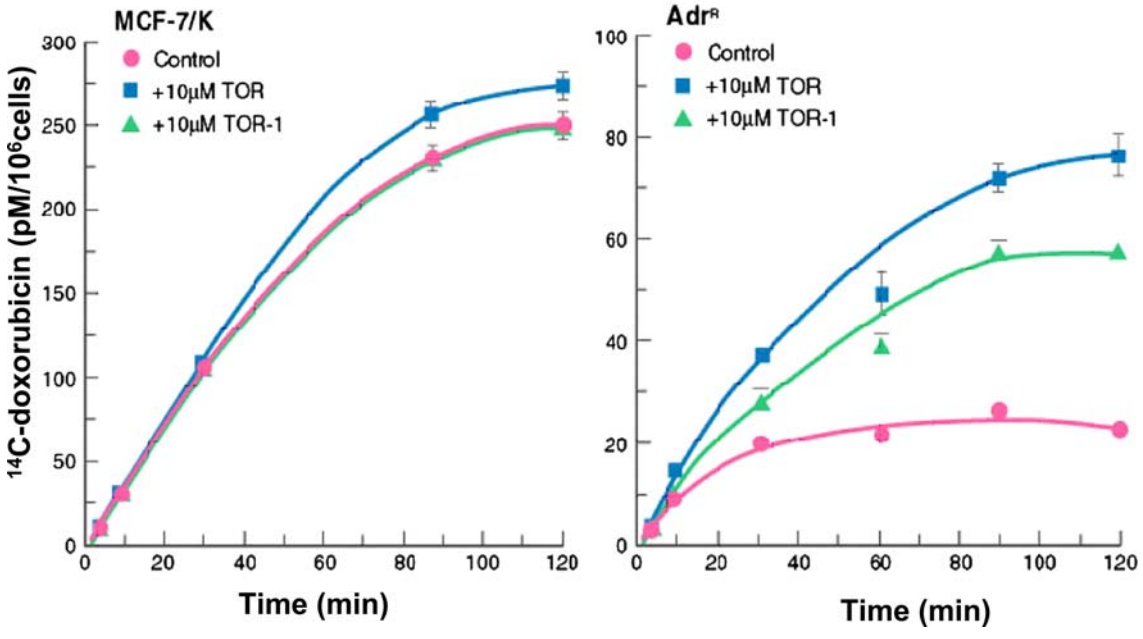

Fig. 3 Toremifene (TOR) and TOR-1 moderated the concentration of ^{14}C-doxorubicin in either parental cell line (MCF-7) or doxorubicin-resistant cell line (Adr^R)

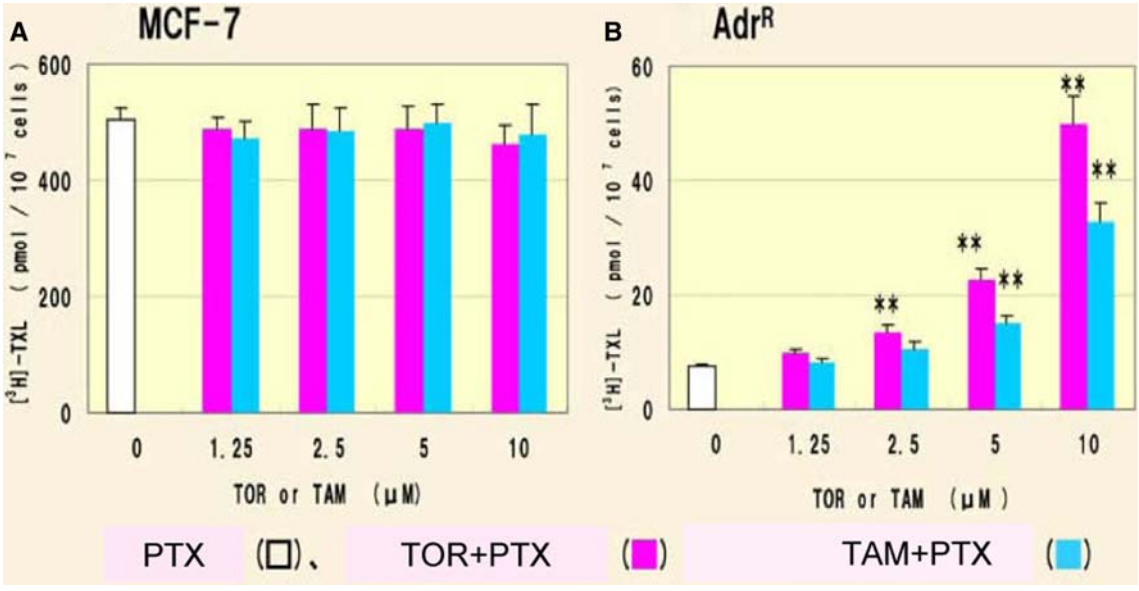

Fig. 4 Toremifene enhances the concentration of ^{3}H-paclitaxel in a MDR cell line. **A** In MCF-7 cell line, base line ^{3}H-paclitaxel was high and did not decrease in the presence and absence of TOR and TAM (tamoxifen). **B** In the Adr^{R} cell line, base line ^{3}H-paclitaxel was low. However, in the presence of TOR or TAM, concentration of ^{3}H-paclitaxel increased in a dose-dependent manner of TOR or TAM. TOR + PTX, toremifene + paclitaxel 1 μM; TAM + PTX, tamoxifen plus paclitaxel 1 μM. $^{**}P < 0.01$ (*t* test). Reprinted with permission from Maruyama et al. [22]

range from 4 to 10 μM (Fig. 4). We evaluated the growth rate and effect of combined treatment. Toremifene demonstrated more synergistic effect when used in combination than tamoxifen to the proliferation of doxorubicin-resistant MCF-7 cells.

Pharmacokinetics and a combination phase I trial of toremifene and paclitaxel

We conducted a combination phase I and pharmacokinetic study to determine the safety and efficacy of this chemoendocrine treatment and to evaluate the drug–drug interactions between paclitaxel and toremifene. Nineteen patients with metastatic breast cancer were enrolled. In the initial phase, patients received paclitaxel 80 mg/m^{2} weekly on days 1, 8, and 15; subsequently, toremifene 120 mg was given from day 18 [20]. On day 32, the patients received paclitaxel l80 mg/m^{2} + toremifene 120 mg. In 15 patients with measurable lesions, there was one partial response, eight cases of stable disease, and six cases of progressive disease. Four patients did not have measurable lesions, but the breast cancer-related symptoms were relieved in all patients. Adverse events did not exceed grade 3 and the addition of toremifene did not enhance the adverse events of paclitaxel. Data for pharmacokinetic parameters were not obtained.

Conclusions

The expression of P-gp encoded by MDR1 mRNA in tumors is associated with clinical drug resistance. P-gp could be an important target to improve the efficacy of chemotherapy.

Dofequidar fumarate is a novel, orally active quinoline derivative that reverses multidrug resistance. Dofequidar enhanced the response to CAF in breast cancer and significantly improved PFS in patients who were premenopausal ($P = 0.046$), who had received no prior therapy ($P < 0.01$), or in patients with advanced (stage IV) primary tumors ($P = 0.017$). Dofequidar may be a promising agent to enhance the efficacy of chemotherapeutic agents.

The antiestrogens may also moderate P-gp-related drug resistance in vitro. Toremifene demonstrated a synergistic effect in combination with paclitaxel on various human breast cancer cell lines. In the clinical setting, combination chemoendocrine therapy of paclitaxel and toremifene may be an attractive strategy for the treatment of breast cancer.

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