Current Topics

Challenges of Drug Delivery Systems That Contribute to Cancer Chemotherapy

Clinical Application of Drug Delivery Systems in Cancer Chemotherapy: Review of the Efficacy and Side Effects of Approved Drugs

Takuya Iwamoto

Department of Pharmacy, Mie University Hospital, Faculty of Medicine, Mie University;
Tsu, Mie 514–8507, Japan.

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In recent years, drug delivery systems (DDS) have been developed, along with anticancer agents for those systems based on the concept of achieving a better clinical response and tolerability. Several clinical trials have shown that these drugs have better clinical effects in the treatment of many cancers, leading to their expanded indications. Liposomal doxorubicin is one DDS agent used to treat AIDS-related Kaposi's sarcoma and ovarian cancer in Japan. In addition to those two indications, the Food and Drug Administration (FDA) approved this drug for the treatment of multiple myeloma in 2007. Another DDS agent approved in Japan is nanoparticle albumin-bound paclitaxel, which has been used in the treatment of breast cancer. Most recently, this drug has been approved for the treatment of non-small cell lung cancer in the U.S.A. Although these DDS agents appear to be less toxic than conventional drugs, DDS-specific side effects such as various skin reactions, hypersensitivity reaction, and peripheral neuropathy sometimes occur. Therefore, medical staff must understand DDS anticancer agents fully, including characteristic side effects, to achieve the desired clinical outcomes.

Key words drug delivery system; liposomal doxorubicin; albumin-bound paclitaxel; side effect

1. INTRODUCTION

Many current anticancer drugs have less than ideal pharmaceutical and pharmacological properties such as low aqueous solubility, irritating nature, lack of stability, rapid metabolism, and nonselective drug distribution. These properties can lead to several adverse consequences, including suboptimal therapeutic activity, dose-limiting side effects, and poor patient quality of life. From the aspect of pharmacokinetics, in particular drug distribution, these may cause low bioavailability of the anticancer drug at the site of action as well as high organ toxicity limiting the maximum tolerated dose. Liposomes and protein-based drug delivery systems (DDS) are archetypal nanoscale DDS.

Doxorubicin HCl liposomal injection (Doxil in the U.S.A. and Japan) was the first nanoscale DDS agent to receive clinical approval for the treatment of AIDS-related Kaposi's sarcoma. Currently, numerous traditional anticancer drugs are encapsulated in liposomes and many of them have been approved for clinical use, as shown in Table 1, or are undergoing clinical trials. In addition, nanoparticle albumin-bound (nab)-paclitaxel (Abraxane in the U.S.A. and Japan) has recently been approved for the treatment of metastatic breast cancer. The DDS anticancer agents were developed based on the concept of achieving a better clinical response and tolerability. However, these drugs are often discontinued due to severe side effects. This paper focuses on liposomal doxorubicin and nab-paclitaxel, which are administered in clinical practice in Japan, including a discussion of the undesirable side effects

when continuing chemotherapy.

2. LIPOSOMAL DOXORUBICIN

2.1. Patients with AIDS-Related Kaposi's Sarcoma In 1998, Stewart *et al.* reported a phase III study that compared liposomal doxorubicin 20 mg/m² given every 3 weeks with the combination of bleomycin and vincristine.¹⁾ That study showed that the liposomal product was an effective treatment for AIDS-related Kaposi's sarcoma ($n=241$) with a higher overall response rate (58.7% vs. 23.3%; $p<0.001$).¹⁾ In the same year, Northfelt *et al.* reported a phase III study that compared liposomal doxorubicin 20 mg/m² given every 2 weeks with bleomycin and vincristine, where patients with liposomal doxorubicin showed a higher overall response rate (45.9% vs. 24.8%; $p<0.001$).²⁾ In 2010, Cianfrocca *et al.* demonstrated in a phase III study that treatment with either paclitaxel or liposomal doxorubicin 20 mg/m² given every 3 weeks appeared to produce comparable response rates (56% vs. 46%; $p=0.486$), median progression-free survival (PFS) (17.5 vs. 12.2 months; $p=0.653$), and 2-year survival rates (79% vs. 78%; $p=0.748$) in patients with advanced, symptomatic, AIDS-associated Kaposi's sarcoma.³⁾ In the U.S.A., doxorubicin HCl liposome injection was approved in 1995 to be administered intravenously at a dose of 20 mg/m² every 3 weeks for as long as patients respond satisfactorily and tolerate treatment. In Japan, doxorubicin HCl liposome injection has been available since 2007 at the same dosage schedule as approved in the U.S.A.

2.2. Patients with Ovarian Cancer In 2001, the results of a phase III study to compare the efficacy of liposomal doxorubicin and topotecan in patients with epithelial ovarian carci-

Table 1. DDS Anticancer Agents Approved in the U.S.A. and/or Japan

Ingredient	Modification	Proprietary name	Indication	Approval (year)		Reference
				U.S.A.	Japan	
Doxorubicin	Liposomal	Doxil	AIDS-related Kaposi's sarcoma	1995	2007	1-3)
			Ovarian cancer (after failure of platinum-based chemotherapy)	1999	2009	4-6)
			Multiple myeloma	2007	—	10, 11)
Daunorubicin	Liposomal	Daunoxome	AIDS-related Kaposi's sarcoma	1996	—	19, 20)
Cytarabine	Liposomal	Depocyt	Lymphomatous meningitis	1999	—	21)
Paclitaxel	Albumin-bound	Abraxane	Metastatic breast cancer	2005	2010	13, 22)
Vincristine	Liposomal	Marqibo	Acute lymphoblastic leukemia	2012	—	23)

noma that had recurred after, or was not responsive to, first-line platinum-based chemotherapy was published by Gordon *et al.*⁴⁾ They concluded that the two regimens had comparable efficacy (overall response rates: 19.7% vs. 17.0%; $p=0.390$).⁴⁾ Based on that phase III study, doxorubicin HCl liposome injection of 50 mg/m² once every 4 weeks was approved in 1995 for the treatment of metastatic carcinoma of the ovary in patients with disease refractory to paclitaxel and platinum-based chemotherapy regimens. In Japan, phase I and phase II study results were reported in 2006⁵⁾ and 2008,⁶⁾ respectively, showing that the recommended dose of liposomal doxorubicin was 50 mg/m² every 4 weeks based on its side effects, the overall response rate to the regimen in patients with epithelial ovarian carcinoma as second- or later-line treatment was 21.9%, and 38.4% of patients had stable disease.^{5,6)} Doxorubicin HCl liposome injection has been available since 2009 and is administered at a dose of 50 mg/m² every 4 weeks in ovarian cancer patients with a previous chemotherapy history in Japan.

Since the approval, much research has been done in phase III studies indicating that liposomal doxorubicin plus carboplatin also has activity as a first-line treatment for advanced or recurrent ovarian cancer, which appears to be comparable in efficacy to standard carboplatin and paclitaxel.⁷⁻⁹⁾

2.3. Patients with Multiple Myeloma Orłowski *et al.* showed in 2007 that liposomal doxorubicin plus bortezomib compared with bortezomib alone improved time to progression (TTP) (9.3 vs. 6.5 months; $p<0.001$) in relapsed or refractory multiple myeloma.¹⁰⁾ A year earlier, in a similar phase III study, Sonneveld *et al.* showed that liposomal doxorubicin plus bortezomib significantly prolonged TTP compared with bortezomib alone (270 vs. 205 d; $p=0.018$) in patients with recurrent or refractory multiple myeloma who had received prior thalidomide/lenalidomide therapy.¹¹⁾ Based on that phase III study, doxorubicin HCl liposome injection at a dose of 30 mg/m² once every 3 weeks concomitantly with bortezomib 1.3 mg/m² bolus on days 1, 4, 8, and 11 was approved in 1997 for the treatment of multiple myeloma patients who had not previously received bortezomib but had received at least one prior therapy regimen. Patients may be treated for up to 8 cycles until disease progression or the occurrence of unacceptable toxicity.

Although liposomal doxorubicin has not been approved for multiple myeloma in Japan, a clinical trial of combination therapy with bortezomib, doxorubicin, and dexamethasone was conducted. In 2010, Takamatsu *et al.* reported phase I study results indicating that bortezomib at the dose of 1.0 mg/m² bolus on days 1, 4, 8, and 11 every 3 weeks was recommended in combination with conventional doxorubicin on

days 1-4.¹²⁾ In addition, a phase II trial to investigate the efficacy and safety of subcutaneous injection of bortezomib combined with conventional doxorubicin and dexamethasone for previously untreated multiple myeloma patients is ongoing (UMIN 000007803).

3. ALBUMIN-BOUND PACLITAXEL

3.1. Patients with Metastatic Breast Cancer The phase III trial that led to the U.S.A. approval of nab-paclitaxel was an international, randomized, open-label study published in 2005.¹³⁾ In that trial, patients were randomly assigned to 3-week cycles of either nab-paclitaxel 260 mg/m² intravenously without premedication ($n=229$) or standard paclitaxel 175 mg/m² intravenously with premedication ($n=225$). nab-Paclitaxel demonstrated significantly higher overall response rates (ORRs) compared with standard paclitaxel (33% vs. 19%, respectively; $p=0.001$) and significantly longer TTP (23.0 vs. 16.9 weeks, respectively; $p=0.006$). Based on that phase III study, nab-paclitaxel (Abraxane) was approved in 2005 for the treatment of metastatic breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months after adjuvant chemotherapy in the U.S.A. In Japan, a phase I trial of nab-paclitaxel was conducted in patients with advanced solid tumors refractory to standard therapy. They received a 30-min intravenous infusion of nab-paclitaxel every 3 weeks without premedication at 200, 260 or 300 mg/m², respectively.¹⁴⁾ Although nab-paclitaxel administered on the every-3-week schedule was well tolerated up to 300 mg/m², the recommended dose was determined to be 260 mg/m² in consideration of efficacy, toxicity, and similarity of pharmacokinetic profile in the international phase III studies.^{13,15)} In Japan, nab-paclitaxel at a dose of 260 mg/m² every 3 weeks was approved for patients with breast cancer in 2010.

3.2. Patients with Non-small Cell Lung Cancer Recently, the results of an international phase III trial comparing the efficacy and safety of nab-paclitaxel plus carboplatin with standard paclitaxel plus carboplatin in advanced non-small-cell lung cancer (NSCLC) have been reported.¹⁶⁾ In that study, 1,052 untreated patients with stage IIIB to IV NSCLC were randomly assigned to receive nab-paclitaxel 100 mg/m² weekly and carboplatin at area under the concentration time curve (AUC) 6 once every 3 weeks or standard paclitaxel 200 mg/m² plus carboplatin AUC 6 once every 3 weeks. The nab-paclitaxel arm demonstrated a significantly higher ORR than the standard paclitaxel arm (33% vs. 25%; $p=0.005$). There was an approximately 10% improvement in the median PFS (6.3 vs. 5.8 months; $p=0.214$) and overall survival rate (12.1

vs. 11.2 months; $p=0.271$) in the nab-paclitaxel arm vs. standard paclitaxel arm, respectively. Patients enrolled in North America showed a significantly increased overall survival rate with nab-paclitaxel vs. standard paclitaxel. Most recently, the administration of nab-paclitaxel 100 mg/m² weekly in combination with carboplatin was approved as first-line therapy in patients with locally advanced or metastatic NSCLC in October 2012.

Japanese institutes (149 patients) participated in the above international phase III trial and they reported significant improvement in median PFS (6.9 vs. 5.6 months) in the nab-paclitaxel arm vs. standard paclitaxel arm.¹⁶⁾ However, no improvement in median overall survival was observed (16.7 vs. 17.2 months) in the nab-paclitaxel arm vs. the standard paclitaxel arm, respectively.¹⁶⁾

4. CHARACTERISTIC SIDE EFFECTS

4.1. Liposomal Doxorubicin Although some studies showed that liposomal doxorubicin is less toxic than other second-line chemotherapy regimens for ovarian cancer, liposome-specific side effects such as various skin and hypersensitivity reactions were reported in addition to severe myelosuppression. A phase II trial in ovarian cancer revealed that asthenia and hand-foot syndrome (HFS) were the two most common adverse events related to liposomal doxorubicin and were seen in 41.6% of patients.⁴⁾ Other adverse events that occurred frequently were nausea (38.2%), neutropenia (37.1%), stomatitis (34.8%), rash (28.1%), mucositis (21.3%), vomiting (19.1%), anorexia (13.5%), and diarrhea (12.4%).⁴⁾ Overall, higher than grade 3 events were noted in 63 patients (70.8%), and HFS (20.2%), anemia (20.2%), and neutropenia (11.2%) were common. Cardiac toxicity appears to be less common and only one patient, an 86-year-old woman who entered the study with a left ventricular ejection fraction of 53%, experienced grade 3 left ventricular dysfunction.¹⁷⁾ An episode of hypersensitivity reaction associated with drug infusion was reported in an ovarian cancer patient during her first cycle of chemotherapy.¹⁷⁾ The Doxil package insert in the U.S.A. and Japan states that the drug should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions.

In the Japanese phase II trial in ovarian cancer previously treated with platinum-based chemotherapy, the major nonhematologic toxicities were HFS (grade 3, 16.2%) and stomatitis (grade 3, 8.1%).⁶⁾ Myelosuppression such as leukopenia (grade 3, 52.7%; grade 4, 6.8%), neutropenia (grade 3, 31.1%; grade 4, 36.5%), and decreased hemoglobin (grade 3, 14.9%; grade 4, 2.7%) were the most common hematologic toxicities.⁶⁾ Liposomal doxorubicin was discontinued due to adverse events in 16 patients (21.6%) due to decreased hemoglobin in 6 patients (8.1%), leukopenia in 4 (5.4%), and HFS and neutropenia in 3 each (4.1%). Administration of the drug was delayed in 49 patients (66.2%) in 111 of 334 cycles due to adverse events, mainly including leukopenia in 68 cycles (20.4%), neutropenia in 56 cycles (16.8%), and HFS in 40 cycles (12.0%).⁶⁾ Liposomal doxorubicin is used in patients with a history of receiving platinum compounds and/or taxanes, and therefore hematopoietic recovery after myelosuppression caused by liposomal doxorubicin must be delayed due to previous chemotherapies.

4.2. Albumin-Bound Paclitaxel Two major disadvantages of the standard taxanes docetaxel and paclitaxel are

the frequency of hypersensitivity reactions and neuropathy. Standard paclitaxel uses Cremophor EL as a solvent, which requires substantial premedication with high doses of steroids and antihistamines, and lengthy infusion times. nab-Paclitaxel was developed to overcome the limitations of standard taxanes, provide more convenient drug administration, and improve toxicity profiles. Initial phase I trials in the U.S.A. investigated the tolerability of nab-paclitaxel on an every-3-week schedule, and the maximum tolerated dose was established at 300 mg/m² every 21 d, with peripheral neuropathy being the dose-limiting toxicity.¹⁸⁾

In the international phase III trial comparing the effects of nab-paclitaxel 300 mg/m² every 21 d and standard paclitaxel 175 mg/m² every 21 d in patients with breast cancer, although the patients in the nab-paclitaxel arm received an average paclitaxel dose intensity 49% greater than that received by patients in the standard paclitaxel arm, treatment compliance was comparable between the two arms (96% vs. 94%, respectively).¹³⁾ In addition, the incidence of grade 4 neutropenia was significantly lower with nab-paclitaxel compared with standard paclitaxel (9% vs. 22%, respectively; $p<0.001$). However, the dose-limiting toxicity of sensory neuropathy (grade 3) was more common in the nab-paclitaxel arm than in the standard paclitaxel arm (10% vs. 2%, respectively; $p<0.001$). On the other hand, another phase III study of NSCLS treatment showed that patients who received nab-paclitaxel 100 mg/m² weekly plus carboplatin AUC 6 developed less grade 3 sensory neuropathy (2%) than those receiving standard paclitaxel 200 mg/m² plus carboplatin every 3 weeks (11%).¹⁶⁾ In that study, only 3% of patients had received prior chemotherapy. Therefore, a prior history of chemotherapy may influence the occurrence of nab-paclitaxel-induced sensory neuropathy as well as dosing schedule.

5. CONCLUSION

In recent years, DDS anticancer agents have received considerable attention. Several phase II and III trials have shown increased clinical efficacy of these drugs. Liposomal doxorubicin and nab-paclitaxel are already available for the treatment of Kaposi's sarcoma, ovarian cancer, and breast cancer in Japan. Although these agents appear to be less toxic than conventional drugs, DDS drug-specific side effects such as skin and hypersensitivity reactions and peripheral neuropathy often occur. Therefore, medical staff must have a thorough understanding of DDS anticancer agents including their characteristic side effects to achieve the desired clinical outcome of treatment.

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