Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
E-mail: jzus@zju.edu.cn

Review:

Use of liposomal doxorubicin for adjuvant chemotherapy of breast cancer in clinical practice*

Ming ZHAO[§1], Xian-feng DING[§1], Jian-yu SHEN[1], Xi-ping ZHANG[†‡2], Xiao-wen DING[‡2], Bin XU[3]

([1]*College of Life Sciences, Zhejiang Sci-Tech University, Hangzhou 310018, China*)

([2]*Department of Tumor Surgery, Zhejiang Cancer Hospital, Hangzhou 310022, China*)

([3]*Institute of Occupational Diseases, Zhejiang Academy of Medical Sciences, Hangzhou 310013, China*)

[†]E-mail: zxp99688@sina.com; 626876448@qq.com

Received Aug. 10, 2016; Revision accepted Oct. 5, 2016; Crosschecked Dec. 12, 2016

Abstract: Breast cancer is one of the malignant tumors with the highest morbidity and mortality. It is helpful to reduce the rate of tumor recurrence and metastasis by treating breast cancer with adjuvant chemotherapy, so as to increase the cure rate or survival of patients. In recent years, liposomes have been regarded as a kind of new carrier for targeted drugs. Being effective for enhancing drug efficacy and reducing side effects, they have been widely used for developing anticancer drugs. As a kind of anthracycline with high anticancer activity, doxorubicin can treat or alleviate a variety of malignant tumors effectively when it is used on its own or in combination with other anticancer drugs. Although liposomal doxorubicin has been extensively used in the adjuvant chemotherapy of breast cancer, its exact therapeutic efficacy and side effects have not been definitely proven. Various clinical studies have adopted different combined regimes, dosages, and staging, so their findings differ to certain extent. This paper reviews the clinical application of liposomal doxorubicin in the adjuvant chemotherapy of breast cancer and illustrates therapeutic effects and side effects of pegylated liposomal doxorubicin (PLD) and non-PLD (NPLD) in clinical research, in order to discuss the strategies for applying these drugs in such adjuvant chemotherapy, looking forward to providing references for related research and clinical treatment in terms of dosage, staging, combined regimes, and analysis methods and so on.

Key words: Liposomal doxorubicin; Breast cancer; Adjuvant chemotherapy; Therapeutic effect; Toxic and side effects
http://dx.doi.org/10.1631/jzus.B1600303 **CLC number:** R979.1+4

1 Introduction

Breast cancer is one of the most common malignant tumors in women. According to a 2014 American Cancer Statistical Research Report (Siegel *et al*., 2014), about 232 700 women suffered from breast cancer, accounting for 29% of all women with cancer and the highest proportion among women with malignant tumors; 40 000 women died of breast cancer, which contributed to 15% cancer deaths and the 2nd highest mortality of cancer among women. Adjuvant chemotherapy means that a tumor is treated by chemical drugs before or after relevant surgery or radiotherapy. Performing systemic and systematic treatment by cytotoxic drugs before surgery or radiotherapy, neoadjuvant chemotherapy has become the foremost choice for locally advanced breast cancer, mainly used for treating patients who have been proven to exhibit lymph node metastasis and wish to conserve their breasts in spite of the impossibility of them undertaking breast conserving surgery (Bear *et al*., 2003).

‡ Corresponding authors
§ The two authors contributed equally to this work
* Project supported by the "151" Excellent Middle-Aged and Talented Young Persons of Zhejiang Province, China (No. 2010382) and the Key Platform Technological Project of Zhejiang Medical Science and Hygiene (No. 2016ZDB003), China
ORCID: Xi-ping ZHANG, http://orcid.org/0000-0002-3556-9681

As an anthracycline and chemotherapeutic drug, doxorubicin was first isolated from *Streptomyces peucetius* (Minotti *et al*., 2004). Drugs with anthracyclines as the active ingredient have been widely used for treating cancer (Hortobágyi, 1997). Clinical research and application revealed that in spite of its potential anticancer effects, doxorubicin is highly toxic, and its long-term application may cause dose-dependent irreversible cardiomyopathy, severe cardiac toxicity, or liver damage, thereby limiting its application in clinical practice (Mitra *et al*., 2001; Greish *et al*., 2004). In subsequent studies, the toxicity of the drug was effectively reduced by changing its dosage (Yoo *et al*., 2002; Yokoyama, 2005), in order that it could be used more widely. Compared with diseases such as ovarian cancer, lymphoma, and leukemia, it is still at an early stage of treating breast cancer by adjuvant chemotherapy with doxorubicin. The therapeutic efficacy, toxicity, and side effects remain to be further analyzed and demonstrated.

As a phospholipid bilayer vesicle like biofilm in structure, liposome was first discovered by Bangham *et al*. (1965). Thereafter, Ryman and Whelan (1971) proposed using liposome as a drug carrier for improving drug targeting and reducing side effects. Subsequently, this drug has been explored increasingly more intensively and gradually more widely used. Current clinical studies have demonstrated that drugs with liposome as a carrier have advantages such as immunogenicity, insignificant toxicity and side effects, as well as easy adsorption (Tyagi *et al*., 2006). At present, doxorubicin, containing liposome as a drug carrier in the treatment of cancer, has been mainly divided into pegylated liposomal doxorubicin (PLD) and non-PLD (NPLD), the major difference being whether a polyethylene glycol-modified agent is contained or not.

2 PLD and adjuvant chemotherapy of breast cancer

PLD has been widely used for treating recurrent ovarian cancer and its efficacy has been generally recognized (Table 1). Clinical application and research on PLD show that it can play a role in treating various malignant tumors including breast cancer. A study found that PLD can extend the disease-free survival (DFS) period for breast cancer patients at pathological stages I–III, suggesting that it may be applicable to the various pathological stages of such cancer treatment (Lu *et al*., 2016).

2.1 Locally advanced or recurrent breast cancer

Many clinical studies confirmed that a combined PLD regime (e.g. with paclitaxel, docetaxel, gamcitabine, and platinum drugs) is more effective for treating patients with human epidermal growth factor receptor 2 (HER-2) positive locally advanced or recurrent breast cancer, and the use of liposome as a carrier may significantly reduce the cardiac toxicity of the drugs. A phase-II study has suggested that after

Table 1 Chemotherapy cycles and combination drugs related to PLD

Dosage (mg/m^2)	Time (week)	Periodicity (cycle)	Drug combination	Entity/pathology	Reference
30	3	6	Gemcitabine+paclitaxel	Locally advanced	Artioli *et al*., 2010
35	3	6	Paclitaxel	Locally advanced	Gogas *et al*., 2002
15	2	8	Paclitaxel	Locally advanced	Rossi *et al*., 2008
35	3	6	Cyclophosphamide+ trastuzumab+paclitaxel	Locally advanced/HER-2 positive	Tuxen *et al*., 2014
20	2	6	Cyclophosphamide	Locally advanced	Dellapasqua *et al*., 2011
25	3	8	Cisplatin+fluorouracil	Locally advanced/HER-2 negative	Torrisi *et al*., 2011
40	3	6	Cyclophosphamide+ fluorouracil	Metastatic	Rau *et al*., 2015
40	4	6	Lapatinib+trastuzumab	Metastatic/HER-2 positive	Pircher *et al*., 2015
30	3	6–8	Docetaxel	Metastatic	Sparano *et al*., 2009
20	2	8		Locally advanced and metastatic	Basso *et al*., 2013
40	4	6	Vinorelbine	Metastatic	Addeo *et al*., 2008
45	4	6	Capecitabine	Metastatic/HER-2 negative	Smorenburg *et al*., 2014

6 cycles of treatment in combination with PLD (administered at 30 mg/m^2 every three weeks), gemcitabine, and paclitaxel, better therapeutic efficacy was detected in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy (Artioli *et al*., 2010). In a phase-II clinical study by Gogas *et al*. (2002) suggested that 71% of patients were remitted after 6 cycles of combined therapy. This research finding further verified the activity of combined PLD and paclitaxel in neoadjuvant chemotherapy of patients with locally advanced breast cancer. Using low-dosage PLD (administered at 15 mg/m^2 every two weeks) in combination with paclitaxel, Rossi *et al*. (2008) evaluated its activity in neoadjuvant chemotherapy. The results suggested that the total effective rate reached 74%. In addition, a phase-II clinical study conducted by Tuxen *et al*. (2014) suggested that the combined use of PLD (administered at 35 mg/m^2 every three weeks) with cyclophosphamide, trastuzumab, and paclitaxel could achieve a total effective rate of 83% for patients with HER-2 positive locally advanced breast cancer. In particular, the expression level of HER-2 turned from positive into negative among a minority of patients, which indicated that this regime exhibited an extremely high pharmaceutical activity. In the above clinical studies, the adverse reactions caused by PLD mainly included hand-foot syndrome, skin toxicity, and mucosal inflammation, all of which were controllable. The patients showed no obvious cardiac toxicity and the total effective rate in the studies reached over 70%. Therefore, it may be generally confirmed that a combined PLD regime is effective and safe for neoadjuvant chemotherapy in such cases.

In addition, Dellapasqua *et al*. (2011) evaluated the role of combined PLD (administered at 20 mg/m^2 every two weeks) and low-dosage cyclophosphamide (50 mg/d) in the preoperative treatment of locally advanced breast cancer. The results suggested that 62.1% patients had partial responses, while the remainder showed no response. With regard to toxic and side effects, there were three patients with skin toxicity and four with hand-foot syndrome. This study showed that this regime was relatively tolerable with fewer toxicity and side effects, but also showed limited therapeutic efficacy, which revealed that it was possibly inapplicable to preoperative treatment. Torrisi *et al*. (2011) used PLD (administered at 25 mg/m^2 every three weeks) in combination with cisplatin and infusional fluoruracil (CCF), evaluating the therapeutic efficacy of this combined regime in adjuvant chemotherapy of patients with HER-2 negative locally advanced and recurrent breast cancer. Clinical responses were detected in 77.5% of enrolled patients, including 3 cases with complete response (7.7%), and it was notable that all three were estrogen receptor (ER) positive. This result reminds us that CCF is possibly effective for increasing the rate of clinical response to PLD, and an ER would strengthen the activity of PLD. Karpinska *et al*. (2015) discovered that among patients with locally advanced breast cancer who undertook neoadjuvant chemotherapy of combined PLD and docetaxol, obesity would significantly reduce their total life span, but did not influence their pathological responses to drugs. All these studies have suggested that the therapeutic efficacy, toxicity, and side effects of PLD are possibly impacted by many factors when it is used for treating locally advanced breast cancer. Deeper exploration and verification will provide more references for the application of PLD in such cases.

Thermotherapy is a therapy that aims to induce apoptosis without injuring normal tissue in view of the differences between normal tissue and tumor cells in their temperature tolerance by heating systemically or locally in the human body with heat energy. In general, it is helpful for enhancing the permeability of liposome in tumor micro-vessels and promoting the accumulation of drugs in tumors (Kong *et al*., 2000). At present, existing research results suggest that it is effective for increasing the therapeutic efficacy of PLD combined with drugs. Vujaskovic *et al*. (2010) performed thermotherapy in combination with PLD and paclitaxel in different doses. The results suggested that when this method was used for neoadjuvant chemotherapy of patients with locally advanced breast cancer, the DFS rate was up to 63% and the overall survival rate reached 75% within four years. In particular, the maximum tolerated dose of both drugs could reach 75 and 175 mg/m^2, respectively. In addition, this study also discovered that patients' pathological response rate was significantly related to thermal dose, perhaps because it was related to tumor vascular permeability and oxygen content being increased by thermotherapy, thus playing its role in strengthening its therapeutic efficacy. Another phase-I

clinical study showed that, for patients with locally recurrent breast cancer, the maximum tolerated dose was 50 mg/m^2 when the low-temperature liposomal doxorubicin was used together with mild local thermotherapy. The main III–IV grades adverse reactions of patients included decreased leucocytes and a total effective rate of 48% (Zagar *et al*., 2014). On the premise of guaranteeing safety, subsequent studies may further explore the optimal combined regime of thermotherapy and PLD.

The results of various clinical studies have suggested that a combined PLD regime exhibits remarkable therapeutic efficacy for treating HER-2 positive and negative breast cancer. Nevertheless, some studies have also shown that for triple negative breast patients, PLD-based adjuvant therapy may be performed as an alternative to those adjuvant therapies without the presence of PLD, but that it may increase hand-foot syndrome (Lien *et al*., 2014). Franchina *et al*. (2012) treated two triple negative breast cancer patients with skin metastasis by combining PLD with gemcitabine. The overall survival of these two patients was extended to 19 and 31 months, respectively. This result suggested that PLD was possibly also effective for treating triple negative breast cancer patients, although this awaits verification.

2.2 Metastatic breast cancer

In spite of its less frequent application in metastatic breast cancer, PLD has been demonstrated to be significantly effective for treating the cancer. For instance, some studies have discovered in mouse models that PLD exhibited better pharmacokinetics than traditional doxorubicin in breast cancer metastasis (Anders *et al*., 2013). Wu *et al*. (2014) discovered in a mouse model that PLD was effective for increasing the efficacy of PLD in delivering PLD and combatting cancer for patients with breast cancer brain metastasis by PLD and short-term focused ultrasound thermotherapy.

Clinical studies have demonstrated the effects of using PLD for adjuvant chemotherapy of advanced and metastatic breast cancer. Rau *et al*. (2015) evaluated the effect and safety of salvage chemotherapy for treating metastatic breast cancer with PLD (40 mg/m^2)+cyclophosphamide (500 mg/m^2) and 5-fluorouracil (500 mg/m^2) with the presence of paclitaxel in a phase-II clinical study. The results showed that the total effective rate was 41.9% among 45 patients, whose median progression-free survival was 8.2 months and total median survival was up to 36.6 months. In another phase-II clinical study, Pircher *et al*. (2015) performed adjuvant chemotherapy for patients with advanced HER-2 positive breast cancer by PLD (administered at 40 mg/m^2 every four weeks) in combination with lapatinib and trastuzumab. The results showed that the total effective rate was 54% among patients, whose median progression-free survival was 5.8 months and median overall survival was 23.3 months. In a phase-III clinical study, Sparano *et al*. (2009) compared the combined PLD (administered at 30 mg/m^2 every three weeks) and docetaxol with the separate use of docetaxol. The results showed that, compared with single use of docetaxol, the combined regime did not only increase the total effective rate from 25% to 36%, but also prolonged the median time to tumor progression from 7.0 to 9.8 months. In all above clinical studies, patients exhibited no evident cardiac toxicity, and controllable hand-foot syndrome was also a toxic and side effect induced by PLD. A phase-II study shows that those patients with metastatic breast cancer treated by many chemotherapies including doxorubicin, taxane, and PLD (25 mg/m^2, once in two weeks), to a certain extent, experience a prolonged survival time with lower toxicity (Jehn *et al*., 2016). It is clear that a combined PLD regime is effective for neoadjuvant chemotherapy of advanced breast cancer.

2.3 Elderly patients

At present, it is still a challenge to determine how to treat elderly patients with breast cancer. Thus, some studies have specially evaluated the role of a combined PLD regime in chemotherapy of elderly patients with breast cancer and adopted dosages similar to other clinical studies. Basso *et al*. (2013) examined the therapeutic efficacy of PLD (administered at 20 mg/m^2 every two weeks) for elderly patients with advanced breast cancer, and all patients enrolled were older than 70 years, among whom the total effective rate was 33.3% and the average median time to tumor progression was 10.3 months. Observed III–IV grades toxic and side effects included a small amount of anemia, mocusal inflammation, infection, pulmonary embolism, but no cardiac toxicity. Addeo *et al*. (2008) evaluated the combined regime of PLD

(administered at 40 mg/m^2 every four weeks) and navelbine (administered at 25 mg/m^2 every four weeks) and its therapeutic efficacy for first-line chemotherapy of elderly patients with metastatic breast cancer. The results showed that the total effective rate was 50% among 34 enrolled patients, among whom 3 patients with complete remission survived for over a year. Neutropenia was observed among these three patients, who had neither other toxic nor side effects. The research suggested that this combined regime was more suitable for elderly patients with metastatic breast cancer. In their phase-III clinical study, Smorenburg *et al*. (2014) compared PLD (administered at 45 mg/m^2 every four weeks) with capecitabine in first-line chemotherapy of elderly patients with metastatic breast cancer in terms of their therapeutic efficacy and safety, while the patients were mostly HER-2 negative. The results indicated that both drugs were similar in therapeutic effects and safety among elderly patients, whereas the patients over 80 years could seldom undertake the chemotherapy.

Research has intensified, and there have been studies aiming to improve the specific application of PLD in adjuvant chemotherapy of breast cancer. For instance, Goel and Gude (2014) discovered that combined PLD and pentoxifylline were effective in combatting breast cancer and cell metastasis in vivo and in vitro. According to numerous studies, when PLD was used for adjuvant chemotherapy of breast cancer, hand-foot syndrome was the major adverse reaction. It was discovered by Templeton *et al*. (2014) that anti-perspirant containing aluminum chloride was effective for alleviating PLD-induced grades II–III hand-foot syndrome. There is still great potential for improving the therapeutic efficacy of PLD for neoadjuvant therapy of breast cancer. Although the toxic and side effects of PLD may be greatly ameliorated by the presence of liposome, it is also necessary to design regimens for alleviating the effects.

3 NPLD and adjuvant chemotherapy of breast cancer

At present, NPLD is mainly aimed at patients with breast cancer, especially those with metastatic breast cancer (Table 2). From a regression analysis, it is clear that it has become one of the most common drugs for first-line chemotherapy of breast cancer in clinical practice. Its toxic and side effects are mostly grades II and III with relatively low cardiac toxicity (Palmieri *et al*., 2014). Different from PLD, NPLD does not contain any poly(ethylene glycol) (PEG) modifier, and exhibits a short half-life in vivo. Therefore, the dosage of NPLD is significantly higher than that of PLD in clinical research and generally ranges from 50 to 70 mg/m^2, administered every three weeks.

3.1 Metastatic breast cancer

3.1.1 HER-2 positive

Studies have shown that the efficacy of PLD is significantly connected with the HER-2 level of patients, and this also seems to be true for NPLD, i.e. its efficacy is more obvious for HER-2 positive patients. In GEICAM 2003-03 research (Antón *et al*., 2011), the combined regime of NPLD (50 mg/m^2)+paclitaxel (60 mg/m^2)+trastuzumab (2 mg/kg) contributed to pathologic complete remission of 42% of patients with HER-2 positive metastatic breast cancer who undertook neoadjuvant chemotherapy, and then 71% of patients received breast conserving surgery.

Table 2 Chemotherapy cycles and combination drugs related to NPLD

Dosage (mg/m^2)	Time (week)	Periodicity (cycle)	Drug combination	Entity/pathology	Reference
50	3	6	Trastuzumab+paclitaxel	Metastatic/HER-2 positive	Antón *et al*., 2011
60	3	6	Trastuzumab+paclitaxel	Metastatic/HER-2 positive	Saracchini *et al*., 2013
50	3	6	Trastuzumab+paclitaxel	Metastatic/HER-2 positive	Gavilá *et al*., 2015
50	3	6	Trastuzumab+paclitaxel	Metastatic/HER-2 positive	Baselga *et al*., 2014
60	3	6	Cyclophosphamide+paclitaxel	Metastatic/HER-2 negative	Vici *et al*., 2014
50–60	3	6	Gemcitabine+paclitaxel	Locally advanced	Schmid *et al*., 2005b
60	3	6	Gemcitabine+paclitaxel	Early stage	Schmid *et al*., 2005a

Detected grades III–IV adverse reactions mainly included neutropenia and fatigue. Grade II cardiac toxicity (declined atrial ejection fraction) was also detected in nine patients, while no heart failure was found. Aiming at patients with HER-2 positive metastatic breast cancer, another phase-II clinical study evaluated the effects of combined NPLD (60 mg/m^2), paclitaxel (60 mg/m^2), and trastuzumab (2 mg/kg) for primary systemic treatment of breast cancer. Among 39 patients, complete remission and partial remission were detected in over 17 and 19 patients, respectively. After medication, possible cardiac toxicity of trastuzumab was not detected among patients (Saracchini *et al*., 2013). Gavilá *et al*. (2015) assessed the therapeutic efficacy and safety of NPLD in neoadjuvant chemotherapy of metastatic breast cancer, including the combination of NPLD (50 mg/m^2) with trastuzumab (2 mg/kg) and paclitaxel (80 mg/m^2). The results suggested that partial remission was detected in 36 patients (63%), and another 12 patients (21%) tended to be partially remitted. Additionally, no cardiac toxicity was detected in those patients. Subsequently, Baselga *et al*. (2014) compared the combined regime of NLDP (50 mg/m^2), trastuzumab (2 mg/kg), and paclitaxel (80 mg/m^2) (MTP group) with trastuzumab combined with paclitaxel (TP group) among patients with HER-2 positive metastatic breast cancer. The median overall survival was 33.6 and 28.9 months for MTP and TP groups, respectively. It is thus clear that NPLD is effective for prolonging the survival of patients. The patients of the MTP group had a little more adverse reactions, but their cardiac toxicity did not increase significantly. In addition, this study also found that NPLD exhibited more remarkable effects in treating receptor ER and progesterone receptor (PR)-negative patients, so more in-depth clinical trials could be conducted. Apparently, without inducing cardiac toxicity, a combined regime of NPLD, trastuzumab, and paclitaxel is highly effective for treating patients with HER-2 positive metastatic breast cancer, and in particular, exhibits a considerably high complete remission rate (Uriarte-Pinto *et al*., 2016).

3.1.2 HER-2 negative

There are relatively few reports on the application of NPLD in the neoadjuvant chemotherapy of patients with HER-2 negative breast cancer, but current studies showed that its efficacy for patients with HER-2 negative breast cancer might be also ideal. Vici *et al*. (2014) evaluated the efficacy of combined NPLD (60 mg/m^2), cyclophosphamide (60 mg/m^2), and paclitaxel (100 mg/m^2) in neoadjuvant chemotherapy of metastatic breast cancer and patients' tolerance to this combined regime. The study included 50 patients with HER-2 negative breast cancer, who were treated through four cycles in total. The results showed that 10 patients achieved pathological complete remission (20.0%) and 35 patients were detected with pathological partial remission (67.5%), among whom, the pathological partial remission rate was 37.5% among patients with triple negative breast cancer. As observed, myelosuppression and hand-foot syndrome were the most frequent toxic and side effects of this combined regime, which had insignificant cardiac toxicity. In the combined regime of this study, cyclophosphamide is used as an alternative to trastuzumab (which is commonly used for chemotherapy of HER-2 positive patients), in order that relatively good effects could be achieved by combined NPLD, cyclophosphamide, and paclitaxel in treating HER-2 negative patients. Provided that this conclusion can be further verified, the application of NPLD in neoadjuvant chemotherapy of breast cancer will be greatly expanded.

In addition, a single-center retrospective analysis showed that NLPD combined with cyclophosphamide was significantly effective for treating brain metastasis in patients with breast cancer (total effective rate of these patients was 50% and overall survival was 23 months) without any grades III–IV adverse reactions (Linot *et al*., 2014). Therefore, this is a viable chemotherapy for such patients before their brain radiotherapy.

3.2 Early or locally advanced breast cancer

Although a combined PLD regime is used as a major alternative in neoadjuvant chemotherapy of early or locally advanced breast cancer, some studies suggested that NPLD is also effective for treating such breast cancer. By retrospective analysis, Davidson *et al*. (2014) evaluated the effectiveness and safety of a combined NPLD regime for treating patients with early breast cancer. The results showed that five-year DFS rate of patients was up to 86% and the mean of left ventricular ejection fraction (LVEF) was still greater than 55%. In addition, the value of

LVEF was not affected by the combined use with trastuzumab nor patients' age. Therefore, better tolerance and efficacy are detected in patients with early breast cancer when NPLD is used. In an earlier phase-I clinical study, a combined regime of NPLD (50–60 mg/m^2)+gemcitabine (350–400 mg/m^2)+ paclitaxel (60–75 mg/m^2) induced clinical remission among 83% of patients with locally advanced breast cancer. In this study, adverse reactions of patients mainly included stomatitis, nausea, diarrhea, infection, and constipation, while heart, kidney, lung, or neurotoxicity was not detected. Therefore, NPLD is considered to be able to enter phase-II clinical research in neoadjuvant chemotherapy of breast cancer (Schmid *et al*., 2005a). In addition, Schmid *et al*. (2005b) found from a phase-II clinical study that a combination of NPLD (60 mg/m^2), paclitaxel (75 mg/m^2), and gemcitabine (350 mg/m^2) in the initial chemotherapy of breast cancer achieved a remission rate of 80% among phases II–III patients, and complete clinical remission was detected in about 25% of patients. In terms of side effects, only above grade III was reached by myelosuppression, and non-hematologic adverse reactions were mild. Hence, this regime is significantly effective for treating early breast cancer and deemed to be suitable for entering the stage of phase-III clinical research.

4 Strategies for applying PLD/NPLD in adjuvant chemotherapy of breast cancer

4.1 Research and application based on *HER-2* gene level

HER-2 gene amplification is one of most important factors that affect breast cancer growth and metastasis, while identification of *HER-2* gene over-expression is also an important index for developing pertinent therapeutic schemes for treating breast cancer. For example, trastuzumab, pertuzumab, and some small molecule tyrosinase inhibitors generally only play roles in HER-2 positive breast cancer patients (Gagliato *et al*., 2016). PLD-related clinical research suggests that PLD is significantly effective in treating both HER-2 positive and negative patients. In general, higher metastases, especially visceral metastasis and brain metastasis, are detected in triple negative breast cancer (O'Reilly *et al*., 2016). Although both PLD and NPLD are found to inhibit tumor metastasis, current research findings showed that the efficacy of PLD in triple negative breast cancer patients is insignificant. NPLD-related clinical studies pay more attention to exploring HER-2 positive metastatic breast cancer, but rarely suggest significant efficacy of NPLD for treating patients with HER-2 negative breast cancer (Linot *et al*., 2014). This remains to be verified by more studies. In fact, although HER-2 level has been adopted as a reference index of doxorubicin in clinical practice, the specific interaction mechanism between both them has not yet been discovered, so the scope of clinical application of PLD/NPLD needs to be further clarified.

4.2 Optimization of combined regime

For cancer chemotherapy, reasonably combined chemotherapy of multiple drugs is significantly more effective than a single drug. At present, a CAF (cyclophosphamide, doxorubicin (adriamycin), and fluorouracil) regime has become one of the internationally recognized regimes with better efficacy in the neoadjuvant chemotherapy of breast cancer. Higher cardiac toxicity is the major problem of this regime. According to many clinical research findings mentioned in this paper, the application of liposome as a carrier may significantly reduce the cardiac toxicity of doxorubicin, so that it can become an effective and safe combined regime. Currently, the optimal combined regimen based on PLD/NPLD needs to be further optimized. Given the different combined regimes of clinical studies, and the fact that the pathological information of patients also differs, it appears to be unreasonable to discuss the optimal combined regime based on such information. Therefore, it would be helpful for developing or optimizing the optimal combined regime based on PLD/NPLD by systematically comparing and exploring multiple combinations.

4.3 Rationalization of dosage and cycle

The most suitable dosage and cycle of PLD/NPLD-based neoadjuvant chemotherapy of breast cancer have not yet been conclusively decided. Most regimes refer to other PLD/NPLD-based therapies to tackle tumors in terms of their dosage and cycle. Based on the above clinical studies, PLD is mainly administered at 15–20 mg/m^2 every two weeks, 25–35 mg/m^2 every three weeks, or 40–45 mg/m^2

every four weeks, while NPLD is primarily administered at 50–70 mg/m^2 every three weeks. Although clinical studies on different dosages and cycles can show a certain effect, determining the optimum dosage and cycle needs further work. In particular, given patients of different pathological statuses or at different stages of chemotherapy, the best dosage and cycle are likely to differ, and the best dosage and cycle under different combination programs may also be different. Therefore, a research program, with systematic comparison on efficacy and side effects of different dosages and cycles to the same class of patients is very important to be able to make the most rational use of PLD/NPLD in neoadjuvant chemotherapy for breast cancer. In addition, the use of PLD/NPLD within the range will not produce serious toxic and side effects, and in clinical studies of using high-dosage PLD/NPLD, the patients' adverse reactions have no significant increase. This suggests that future clinical studies can try adding a small dosage in order to achieve better efficacy without compromising safety.

4.4 Molecular index and prognosis

At the molecular level, the malignancy of breast cancer, the possibilities of invasion, recurrence, and metastasis as well as the prognosis are evaluated, in order to make up for the deficiencies of prognostic evaluation in the clinical setting and pathology. This can provide evidence for further developing reasonable regimes for adjuvant therapies. In recent years, researchers have discovered from pathological typing that many kinds of molecules can be used as prognostic indicators of neoadjuvant chemotherapy of breast cancer. For instance, over-expression of FOXA1 protein and BCL-2 protein are deemed to be negatively correlated to prognosis of ER positive breast cancer and triple negative breast cancer (Abdel-Fatah *et al*., 2013; Xu *et al*., 2015), while over-expression of the LC3B protein is considered to have a positive correlation with the prognosis of locally advanced breast cancer (Chen *et al*., 2013).

At present, although a lot of molecular prognostic indices of neoadjuvant chemotherapy for breast cancer have been found, very few studies have focused on exploring those indices in a single regime. In terms of doxorubicin, Kim *et al*. (2015) studied and proposed that *ABCB1* gene polymorphism may be considered as a prognostic index of patients with breast cancer undertaking combined PLD and docetaxel neoadjuvant chemotherapy. This study found that the 3435TT subtype of *ABCB1* gene contributed to a longer overall survival of patients after their treatment. More studies of this type would provide more references for rational improvement of neoadjuvant chemotherapy with the presence of liposomal doxorubicin.

4.5 Statistical analysis based on a large number of samples

Although clinical experimental results on small samples have shown the roles of PLD/NPLD in neoadjuvant chemotherapy of breast cancer, there are differences among the results, and the evaluation criteria are not the same in each case. Therefore, the results of statistical analysis incorporating several studies are highly valuable as a reference. For example, the latest meta-analysis suggested that patients' total effective rate in LD-based neoadjuvant chemotherapy of breast cancer was significantly higher compared with traditional chemotherapy with doxorubicin, and the cardiac toxicity of the chemotherapy declined significantly (Xing *et al*., 2015). Furthermore, the progression-free survival and total survival of patients increased when liposomal doxorubicin was used, whereas it showed no significant statistical difference from traditional therapy with doxorubicin. Another meta-analysis suggests that, compared to the animal model, the effect of PLD is not significantly enhanced compared with the traditional doxorubicin, and an optimized dosage regimen and method are still needed (Petersen *et al*., 2016). With the performance of ongoing clinical studies, different objects may be set for comparison in such analysis, so as to obtain more valuable information, which may be further verified by pertinent clinical studies.

5 Conclusions

Anthracyclines play important roles in neoadjuvant chemotherapy of breast cancer, where the combination with doxorubicin is one of the major medication strategies. Although their efficacy has been fully recognized, some problems that emerge during the medication remain to be solved, including the side effects of cardiac toxicity. However, the

application of liposomes as carriers can, to a considerable extent, solve these problems. By reviewing numerous clinical research findings, it can be seen that the toxic and side effects of chemotherapy with PLD mainly include myelosuppression, hand-foot syndrome, and stomatitis, all of which can be effectively controlled (Duggan and Keating, 2011). Likewise, NPLD clinical studies also consistently show that PLD does not have obvious cardiac toxicity. The efficacy of a combined PLD/NPLD regime in the neoadjuvant chemotherapy of breast cancer is also affirmed by clinical studies, especially for patients with an HER-2 positive receptor. PLD and NPLD have been examined in corresponding clinical studies in each pathological stage of breast cancer, and both of them exhibited good efficacy in most physiological stages. In 2010, some oncologists, pharmacologists and cardiologists held a meeting in Florence, Italy and reached a consensus that PLD/NPLD should be used for treating tumors like breast cancer in place of traditional doxorubicin (Airoldi *et al*., 2011).

On the other hand, current PLD/NPLD clinical studies also have some limitations. Firstly, the combined regime, dosage, patients' pathological information, and evaluation methods of various studies are different. It is difficult to know which regime is most effective for treating patients with breast cancer whose pathological typing differs, so the possibility of improvement of the medication is limited. Secondly, the sample size of clinical studies is generally small and research findings are influenced by many factors. In this case, the conclusions could be inconsistent with the real situation because of random errors. In addition, the specific mechanism of the role of PLD/NPLD in breast cancer treatment remains unclear, so there is a lack of powerful theoretical support for all research findings. Univariate comparative research, data analysis of numerous data, and further fundamental research will be helpful in solving the above problems. In summary, new anthracyclines, PLD and NPLD, significantly reduce toxic and side effects while maintaining their efficacy, and it is expected to become one of drugs indispensable for adjuvant chemotherapy of breast cancer.

Compliance with ethics guidelines

Ming ZHAO, Xian-feng DING, Jian-yu SHEN, Xi-ping ZHANG, Xiao-wen DING, and Bin XU declare that they have no conflict of interest.

The article does not contain any studies with human or animal subjects performed by any of the authors.

References

Abdel-Fatah, T.M., Perry, C., Dickinson, P., *et al*., 2013. Bcl2 is an independent prognostic marker of triple negative breast cancer (TNBC) and predicts response to anthracycline combination (ATC) chemotherapy (CT) in adjuvant and neoadjuvant settings. *Ann. Oncol.*, **24**(11):2801-2807. http://dx.doi.org/10.1093/annonc/mdt277

Addeo, R., Faiola, V., Guarrasi, R., *et al*., 2008. Liposomal pegylated doxorubicin plus vinorelbine combination as first-line chemotherapy for metastatic breast cancer in elderly women > or =65 years of age. *Cancer Chemother. Pharmacol.*, **62**(2):285-292. http://dx.doi.org/10.1007/s00280-007-0605-6

Airoldi, M., Amadori, D., Barni, S., *et al*., 2011. Clinical activity and cardiac tolerability of non-pegylated liposomal doxorubicin in breast cancer: a synthetic review. *Tumori*, **97**(6):690-692.

Anders, C.K., Adamo, B., Karginova, O., *et al*., 2013. Pharmacokinetics and efficacy of PEGylated liposomal doxorubicin in an intracranial model of breast cancer. *PLoS ONE*, **8**(5):e61359. http://dx.doi.org/10.1371/journal.pone.0061359

Antón, A., Ruiz, A., Plazaola, A., *et al*., 2011. Phase II clinical trial of liposomal-encapsulated doxorubicin citrate and docetaxel, associated with trastuzumab, as neoadjuvant treatment in stages II and IIIA HER-2-overexpressing breast cancer patients. GEICAM 2003-03 study. *Ann. Oncol*., **22**(1):74-79. http://dx.doi.org/10.1093/annonc/mdq317

Artioli, G., Mocellin, S., Borgato, L., *et al*., 2010. Phase II study of neoadjuvant gemcitabine, pegylated liposomal doxorubicin, and docetaxel in locally advanced breast cancer. *Anticancer Res.*, **30**(9):3817-3821.

Bangham, A.D., Standish, M.M., Watkins, J.C., 1965. Diffusion of univalent ions across the lamellae of swollen phospholipids. *J. Mol. Biol*., **13**(1):238-252. http://dx.doi.org/10.1016/S0022-2836(65)80093-6

Baselga, J., Manikhas, A., Cortés, J., *et al*., 2014. Phase III trial of nonpegylated liposomal doxorubicin in combination with trastuzumab and paclitaxel in HER-2-positive metastatic breast cancer. *Ann. Oncol.*, **25**(3):592-598. http://dx.doi.org/10.1093/annonc/mdt543

Basso, U., Roma, A., Brunello, A., *et al*., 2013. Bi-weekly liposomal doxorubicin for advanced breast cancer in elderly women (≥70 years). *J. Geriatr. Oncol*., **4**(4):340-345. http://dx.doi.org/10.1016/j.jgo.2013.07.004

Bear, H.D., Anderson, S., Brown, A., *et al*., 2003. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J. Clin. Oncol*., **21**(22):4165-4174. http://dx.doi.org/10.1200/JCO.2003.12.005

Chen, S., Jiang, Y.Z., Huang, L., *et al*., 2013. The residual tumor autophagy marker LC3B serves as a prognostic marker in local advanced breast cancer after neoadjuvant chemotherapy. *Clin. Cancer Res*., **19**(24):6853-6862. http://dx.doi.org/10.1158/1078-0432.CCR-13-1617

Davidson, N., Camburn, T., Keary, I., *et al*., 2014. Substituting doxorubicin with nonpegylated liposomal doxorubicin for the treatment of early breast cancer: results of a retrospective study. *Int. J. Breast Cancer*, **2014**:984067. http://dx.doi.org/10.1155/2014/984067

Dellapasqua, S., Mazza, M., Rosa, D., *et al*., 2011. Pegylated liposomal doxorubicin in combination with low-dose metronomic cyclophosphamide as preoperative treatment for patients with locally advanced breast cancer. *Breast*, **20**(4):319-323. http://dx.doi.org/10.1016/j.breast.2011.02.014

Duggan, S.T., Keating, G.M., 2011. Pegylated liposomal doxorubicin: a review of its use in metastatic breast cancer, ovarian cancer, multiple myeloma and AIDS-related Kaposi's sarcoma. *Drugs*, **71**(18):2531-2558. http://dx.doi.org/10.2165/11207510-000000000-00000

Franchina, T., Adamo, B., Ricciardi, G.R., *et al*., 2012. Activity of pegylated liposomal doxorubicin in combination with gemcitabine in triple negative breast cancer with skin involvement: two case reports. *Cancer Biol. Ther.*, **13**(7):472-476. http://dx.doi.org/10.4161/cbt.19593

Gagliato, D.M., Jardim, D.L., Marchesi, M.S., *et al*., 2016. Mechanisms of resistance and sensitivity to anti-HER2 therapies in HER2+ breast cancer. *Oncotarget*, **7**(39):64431-64446. http://dx.doi.org/10.18632/oncotarget.7043

Gavilá, J., Guerrero, Á., Climent, M.Á., *et al*., 2015. Efficacy and safety of neoadjuvant chemotherapy with concurrent liposomal-encapsulated doxorubicin, paclitaxel and trastuzumab for human epidermal growth factor receptor 2-positive breast cancer in clinical practice. *Int. J. Clin. Oncol*., **20**(3):480-489. http://dx.doi.org/10.1007/s10147-014-0727-x

Goel, P.N., Gude, R.P., 2014. Delineating the anti-metastatic potential of pentoxifylline in combination with liposomal doxorubicin against breast cancer cells. *Biomed. Pharmacother.*, **68**(2):191-200. http://dx.doi.org/10.1016/j.biopha.2013.11.003

Gogas, H., Papadimitriou, C., Kalofonos, H.P., *et al*., 2002. Neoadjuvant chemotherapy with a combination of pegylated liposomal doxorubicin (Caelyx) and paclitaxel in locally advanced breast cancer: a phase II study by the Hellenic Cooperative Oncology Group. *Ann. Oncol*., **13**(11):1737-1742. http://dx.doi.org/10.1093/annonc/mdf284

Greish, K., Sawa, T., Fang, J., *et al*., 2004. SMA-doxorubicin, a new polymeric micellar drug for effective targeting to solid tumours. *J. Control. Release*, **97**(2):219-230. http://dx.doi.org/10.1016/j.jconrel.2004.03.027

Hortobágyi, G.N., 1997. Anthracyclines in the treatment of cancer. An overview. *Drugs*, **54**(Suppl. 4):1-7. http://dx.doi.org/10.2165/00003495-199700544-00003

Jehn, C.F., Hemmati, P., Lehenbauer-Dehm, S., *et al*., 2016. Biweekly pegylated liposomal doxorubicin (Caelyx) in heavily pretreated metastatic breast cancer: a phase 2 study. *Clin. Breast Cancer*, **16**(6):514-519. http://dx.doi.org/10.1016/j.clbc.2016.06.001

Karpinska, A., Safranow, K., Kładny, J., *et al*., 2015. The influence of obesity on results of AT (doxorubicin plus docetaxel) neoadjuvant chemotherapy in locally advanced breast cancer patients. *Pol. Przegl. Chir*., **87**(5):231-237.

Kim, H.J., Im, S.A., Keam, B., *et al*., 2015. *ABCB1* polymorphism as prognostic factor in breast cancer patients treated with docetaxel and doxorubicin neoadjuvant chemotherapy. *Cancer Sci.*, **106**(1):86-93. http://dx.doi.org/10.1111/cas.12560

Kong, G., Anyarambhatla, G., Petros, W.P., *et al*., 2000. Efficacy of liposomes and hyperthermia in a human tumor xenograft model: importance of triggered drug release. *Cancer Res.*, **60**(24):6950-6957.

Lien, M.Y., Liu, L.C., Wang, H.C., *et al*., 2014. Safety and efficacy of pegylated liposomal doxorubicin-based adjuvant chemotherapy in patients with stage I–III triple-negative breast cancer. *Anticancer Res.*, **34**(12):7319-7326.

Linot, B., Campone, M., Augereau, P., *et al*., 2014. Use of liposomal doxorubicin cyclophosphamide combination in breast cancer patients with brain metastases: a monocentric retrospective study. *J. Neuro-Oncol.*, **117**(2):253-259. http://dx.doi.org/10.1007/s11060-014-1378-5

Lu, Y.C., Ou-Yang, F., Hsieh, C.M., *et al*., 2016. Pegylated liposomal doxorubicin as adjuvant therapy for stage I-III operable breast cancer. *In Vivo*, **32**(2):159-163.

Minotti, G., Menna, P., Salvatorelli, E., *et al*., 2004. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. *Pharmacol. Rev.*, **56**(2):185-229. http://dx.doi.org/10.1124/pr.56.2.6

Mitra, S., Gaur, U., Ghosh, P.C., *et al*., 2001. Tumour targeted delivery of encapsulated dextran-doxorubicin conjugate using chitosan nanoparticles as carrier. *J. Control. Release*, **74**(1-3):317-323. http://dx.doi.org/10.1016/S0168-3659(01)00342-X

O'Reilly, E.A., Gubbins, L., Sharma, S., *et al*., 2016. The fate of chemoresistance in triple negative breast cancer (TNBC). *BBA Clin*., **3**(3):257-275.

Palmieri, C., Misra, V., Januszewski, A., *et al*., 2014. Multicenter experience of nonpegylated liposomal doxorubicin use in the management of metastatic breast cancer. *Clin. Breast Cancer*, **14**(2):85-93. http://dx.doi.org/10.1016/j.clbc.2013.10.011

Petersen, G.H., Alzghari, S.K., Chee, W., *et al*., 2016. Meta-analysis of clinical and preclinical studies comparing the anticancer efficacy of liposomal versus conventional non-liposomal doxorubicin. *J. Control. Release*, **232**:255-264.

http://dx.doi.org/10.1016/j.jconrel.2016.04.028

Pircher, M., Mlineritsch, B., Fridrik, M.A., *et al*., 2015. Lapatinib-plus-pegylated liposomal doxorubicin in advanced HER-2-positive breast cancer following trastuzumab: a phase II trial. *Anticancer Res*., **35**(1):517-521.

Rau, K.M., Lin, Y.C., Chen, Y.Y., *et al*., 2015. Pegylated liposomal doxorubicin (Lipo-Dox®) combined with cyclophosphamide and 5-fluorouracil is effective and safe as salvage chemotherapy in taxane-treated metastatic breast cancer: an open-label, multi-center, non-comparative phase II study. *BMC Cancer*, **15**:423-431.
http://dx.doi.org/10.1186/s12885-015-1433-4

Rossi, D., Baldelli, A.M., Casadei, V., *et al*., 2008. Neoadjuvant chemotherapy with low dose of pegylated liposomal doxorubicin plus weekly paclitaxel in operable and locally advanced breast cancer. *Anti-Cancer Drugs*, **19**(7):733-737.
http://dx.doi.org/10.1097/CAD.0b013e3283043585

Ryman, B.E., Whelan, W.J., 1971. New aspects of glycogen metabolism. *Adv. Enzymol. Relat. Areas Mol. Biol.*, **34**(4):285-443.
http://dx.doi.org/10.1002/9780470122792.ch6

Saracchini, S., Foltran, L., Tuccia, F., *et al*., 2013. Phase II study of liposome-encapsulated doxorubicin plus cyclophosphamide, followed by sequential trastuzumab plus docetaxel as primary systemic therapy for breast cancer patients with HER-2 overexpression or amplification. *Breast*, **22**(6):1101-1107.
http://dx.doi.org/10.1016/j.breast.2013.09.001

Schmid, P., Krocker, J., Schulz, C.O., *et al*., 2005a. Primary chemotherapy with gemcitabine, liposomal doxorubicin and docetaxel in patients with locally advanced breast cancer: results of a phase I trial. *Anti-Cancer Drugs*, **16**(1):21-29.
http://dx.doi.org/10.1097/00001813-200501000-00003

Schmid, P., Krocker, J., Jehn, C., *et al*., 2005b. Primary chemotherapy with gemcitabine as prolonged infusion, non-pegylated liposomal doxorubicin and docetaxel in patients with early breast cancer: final results of a phase II trial. *Ann. Oncol.*, **16**(10):1624-1631.
http://dx.doi.org/10.1093/annonc/mdi321

Siegel, R., Ma, J., Zou, Z.H., 2014. Cancer statistics, 2014. *CA Cancer J. Clin*., **64**(1):9-29.
http://dx.doi.org/10.3322/caac.21208

Smorenburg, C.H., de Groot, S.M., van Leeuwen-Stok, A.E., *et al*., 2014. A randomized phase III study comparing pegylated liposomal doxorubicin with capecitabine as first-line chemotherapy in elderly patients with metastatic breast cancer: results of the OMEGA study of the Dutch Breast Cancer Research Group BOOG. *Ann. Oncol*., **25**(3):599-605.
http://dx.doi.org/10.1093/annonc/mdt588

Sparano, J.A., Makhson, A.N., Semiglazov, V.F., *et al*., 2009. Pegylated liposomal doxorubicin plus docetaxel significantly improves time to progression without additive cardiotoxicity compared with docetaxel monotherapy in patients with advanced breast cancer previously treated with neoadjuvant-adjuvant anthracycline therapy: results from a randomized phase III study. *J. Clin. Oncol*., **27**(27):4522-4529.
http://dx.doi.org/10.1200/JCO.2008.20.5013

Templeton, A.J., Ribi, K., Surber, C., *et al*., 2014. Prevention of palmar–plantar erythrodysesthesia with an antiperspirant in breast cancer patients treated with pegylated liposomal doxorubicin (SAKK 92/08). *Breast*, **23**(3):244-249.
http://dx.doi.org/10.1016/j.breast.2014.02.005

Torrisi, R., Montagna, E., Scarano, E., *et al*., 2011. Neoadjuvant pegylated liposomal doxorubicin in combination with cisplatin and infusional fluoruracil (CCF) with and without endocrine therapy in locally advanced primary or recurrent breast cancer. *Breast*, **20**(1):34-38.
http://dx.doi.org/10.1016/j.breast.2010.06.005

Tuxen, M.K., Cold, S., Tange, U.B., *et al*., 2014. Phase II study of neoadjuvant pegylated liposomal doxorubicin and cyclophosphamide±trastuzumab followed by docetaxel in locally advanced breast cancer. *Acta Oncol*., **53**(10):1440-1445.
http://dx.doi.org/10.3109/0284186X.2014.921727

Tyagi, P., Wu, P.C., Chancellor, M., *et al*., 2006. Recent advances in intravesical drug/gene delivery. *Mol. Pharm*., **3**(4):369-379.
http://dx.doi.org/10.1021/mp060001j

Uriarte-Pinto, M., Escolano-Pueyo, Á., Gimeno-Ballester, V., *et al*., 2016. Trastuzumab, non-pegylated liposomal-encapsulated doxorubicin and paclitaxel in the neoadjuvant setting of HER-2 positive breast cancer. *Int. J. Clin. Pharm.*, **38**(2):446-453.
http://dx.doi.org/10.1007/s11096-016-0278-5

Vici, P., Pizzuti, L., Gamucci, T., *et al*., 2014. Non-pegylated liposomal doxorubicin cyclophosphamide in sequential regimens with taxanes as neoadjuvant chemotherapy in breast cancer patients. *J. Cancer*, **5**(6):398-405.
http://dx.doi.org/10.7150/jca.9132

Vujaskovic, Z., Kim, D.W., Jones, E., *et al*., 2010. A phase I/II study of neoadjuvant liposomal doxorubicin, paclitaxel, and hyperthermia in locally advanced breast cancer. *Int. J. Hyperthermia*, **26**(5):514-521.
http://dx.doi.org/10.3109/02656731003639364

Wu, S.K., Chiang, C.F., Hsu, Y.H., *et al*., 2014. Short-time focused ultrasound hyperthermia enhances liposomal doxorubicin delivery and antitumor efficacy for brain metastasis of breast cancer. *Int. J. Nanomed.*, **9**(9):4485-4494.

Xing, M., Yan, F., Yu, S., *et al*., 2015. Efficacy and cardiotoxicity of liposomal doxorubicin-based chemotherapy in advanced breast cancer: a meta-analysis of ten randomized controlled trials. *PLoS ONE*, **10**(7):e0133569.
http://dx.doi.org/10.1371/journal.pone.0133569

Xu, S., Wei, Q., Guo, J., *et al*., 2015. FOXA1 expression significantly predict response to chemotherapy in estrogen receptor-positive breast cancer patients. *Ann. Surg. Oncol*., **22**(6):2034-2039.
http://dx.doi.org/10.1245/s10434-014-4313-2

Yokoyama, M., 2005. Drug targeting with nano-sized carrier

systems. *J. Artif. Organs*, **8**(2):77-84. http://dx.doi.org/10.1007/s10047-005-0285-0

Yoo, H.S., Lee, E.A., Park, T.G., 2002. Doxorubicin-conjugated biodegradable polymeric micelles having acid-cleavable linkages. *J. Control. Release*, **82**(1):17-27. http://dx.doi.org/10.1016/S0168-3659(02)00088-3

Zagar, T.M., Vujaskovic, Z., Formenti, S., *et al*., 2014. Two phase I dose-escalation/pharmacokinetics studies of low temperature liposomal doxorubicin (LTLD) and mild local hyperthermia in heavily pretreated patients with local regionally recurrent breast cancer. *Int. J. Hyperthermia*, **30**(5):285-294. http://dx.doi.org/10.3109/02656736.2014.936049

中文概要

题　目：多柔比星脂质体在乳腺癌辅助化疗中的临床应用

概　要：通过综述多柔比星脂质体在乳腺癌辅助化疗中的临床应用，分别阐述临床研究中聚乙二醇多柔比星脂质体（PLD）与非聚乙二醇多柔比星脂质体（NPLD）的治疗效果及毒副作用。进而探讨其在乳腺癌辅助化疗中的使用策略，在用药剂量、分期、联合方案及分析方法等方面，为相关研究及临床治疗提供有价值的参考。

关键词：多柔比星脂质体；乳腺癌；辅助化疗；疗效；毒副作用