Scientific Research Publishing

Open Journal of Blood Diseases, 2023, 13, 51-58
https://www.scirp.org/journal/ojbd
ISSN Online: 2164-3199
ISSN Print: 2164-3180

The Applications of Mitoxantrone and Its Liposome in Adult Acute Myeloid Leukemia

Guancheng Song, Jiaqi Gu, Ying Chen, Yanfang Zhang, Xi Huang, Shifeng Lou, Jianchuan Deng*

Department of Hematology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China
Email: *dengjccq@hospital.cqmu.edu.cn

How to cite this paper: Song, G.C., Gu, J.Q., Chen, Y., Zhang, Y.F., Huang, X., Lou, S.F. and Deng, J.C. (2023) The Applications of Mitoxantrone and Its Liposome in Adult Acute Myeloid Leukemia. *Open Journal of Blood Diseases*, **13**, 51-58.
https://doi.org/10.4236/ojbd.2023.131007

Received: February 5, 2023
Accepted: March 21, 2023
Published: March 24, 2023

Abstract

Acute myeloid leukemia (AML), a rapidly progressing hematopoietic malignancy, can only be cured hopefully by hematopoietic stem cells transplantation (HSCT). Before HSCT, we usually exert effects by attempting certain regimens to induce these tumor cells to death. Administered in AML patients, the classic "3 + 7" intensive induction regimen including anthracyclines and cytarabine is recommended by guidelines worldwide. However, conventional regimens consist of anthracyclines, a category of drug limited by cumulative, dose-related, progressive myocardial damage and congestive heart failure occurs when its total doses break through the cut-off. Based on this background, mitoxantrone (MIT), an anthraquinone, was developed to a new form to reduce cardiotoxicity. Meanwhile, the nanomedicine, mitoxantrone liposome (Lipo-MIT), was characterized by improved bioavailability and limited toxicity. This drug has great therapeutic potential, but different side effects. We conclude the overall history and development of MIT and Lipo-MIT, which show controversial efficacy of MIT compared to doxorubicin and therapeutic potential of Lipo-MIT. This article reviewed the application of MIT and liposome forms in adult AML patients.

Keywords

Acute Myeloid Leukemia, Liposomal Mitoxantrone, Toxicity, Anthracyclines

1. Introduction

AML is a form of cancer that is characterized by infiltration of the bone marrow, blood, and other tissues by proliferative, clonal, abnormally differentiated, and occasionally poorly differentiated cells of the hematopoietic system [1]. Accompanied by changes of cytogenetics, gene mutations, cluster of differentiation, morphology and one or multiple lineage cytopenia, most patients have poor

prognosis in the early years. These leukemia stem cells were shown to reside at the apex of a cellular hierarchy that initiates and maintains the disease, exhibiting properties of self-renewal, cell cycle quiescence, and chemoresistance. In the mid-1990s, both groups, the Italian and French groups, discovered an identical novel compound at much the same time, and they finally gave it the name, daunorubicin [2]. But unfortunately, daunorubicin was demonstrated to have cytotoxic and cardiotoxic effect in 1964 and 1967, respectively [3] [4]. Therefore, doxorubicin, trade name Adriamycin™, the 14-hydroxy derivative of daunomycin, was discovered and displayed superior spectrum of anticancer activity [5] [6] [7]. Though conditions were different between two research, results reported that estimated cumulative 7% to 26% of the recipients would experience doxorubicin-related congestive heart failure at a cumulative dose of 550 mg/m^2 [8] [9]. As an analog of daunorubicin, doxorubicin exposed similar cardiotoxic effect which was paid enough attention to. Obvious flaws made researchers modify the structure of the drug to reduce myocardial toxicity without anticancer activity losses. Consequently, Murdock *et al.* noted a lead compound, 1,4-bis-[[2-(dimethylamino)ethyl]-amino]-9,10-anthracenedione, which have been used as dyes or pigments because of their high chemical, photochemical and thermal stability [10] [11]. In 1979, Murdock *et al.* modified this lead compound and discovered mitoxantrone, trade name Novantrone™, which showed significant objective results in subsequent leukemia trials [12].

2. Clinical Application

With aggressive induction chemotherapy (usually cytarabine and daunorubicin), complete remission (CR) rates fluctuate between 50% and 80% in AML patients, but this number reduced to less than 30% in relapsed patients after salvage regimen [13] [14]. MIT causes slightly reduced cardiotoxicity than doxorubicin and showed comparable anticancer activity [2] [15]. Thereby, mitoxantrone is enrolled in various regimens consisting of inducing and intensive consolidation chemotherapy to treat AML. Meanwhile, mitoxantrone is applied in multiple sclerosis, advanced breast cancer, hormone-resistant prostate cancer and ovarian cancer [16] [17] [18] [19]. In newly diagnosed AML patients, combining MIT (bolus or continuous infusion) with etoposide is an effective first-line therapy [20]. Plenty of literature research data supported that treatment regimens of AML including MIT showed better CR rates than conventional DNA topoisomerase II poison, daunorubicin. Patients with high-risk AML, defined as those with advanced age, relapsed/refractory disease, unfavorable molecular and cytogenetic abnormalities, therapy-related myeloid neoplasm (t-MN) and multiple medical co-morbidities tend to respond poorly to standard cytarabine and daunorubicin induction therapy and have a poor prognosis. In the research by Sarah M. Larson *et al.* [21], combining high-dose cytarabine with MIT was administered in 78 cases with high-risk AML and 45% of them achieved CR, 9% of them died during induction. Combining high dose cytarabine with MIT was proved to be an effective

and well tolerated alternative to standard dose cytarabine with an anthracycline in unfavorable prognosis population. Similar research showed that MIT 8 - 12 mg/m^2 per day yielded higher CR rates compared with DNR at doses of 30 - 50 mg/m^2 [22] [23]. In the research by Löwenberg *et al.* [23], 247 patients were enrolled in MTZ group, 242 patients were enrolled in DNR (daunorubicin) group. In this study, MTZ chemotherapy schedule provided for better complete response rates (MTZ 47% vs DNR 38%), however, overall survival and DFS probabilities did not improve. Marconi *et al.* [24] collected data of 55 patients who had an AML relapse or chemotherapy resistance received MEC (mitoxantrone, etoposide, cytarabine) chemotherapy. Twenty-five patients (45.4%) achieved CR and four patients (7.3%) died, which showed similar outcomes like above. Franco Mandelli *et al.* [25] found that patients had similar CR rates (69%) in three groups (ARA + ETO + DNR/MXR/IDA), but the disease-free survival and survival from CR were longer in the mitoxantrone and idarubicin arms than in the daunorubicin arm (37%, 37%, 29%). In some other literature of higher evidence, meta-analysis by Lei Deng *et al.* [26] showed that compared to daunorubicin, mitoxantrone can significantly improve CR and DFS in patients of all ages. However, death rates during induction therapy and overall survival were proved to be no differences between the two drugs. It was interesting to note that the CR rate for mitoxantrone was significantly higher than that of daunorubicin in the ratio of daunorubicin dose to mitoxantrone dose (D/M) < 4 subgroup during induction therapy. In contrast, there was no difference in CR rate in the D/M > 4 subgroup. Part of favorable regimens in treating AML patients are collected in the following **Table 1**, and the application of this drug may need further breakthrough.

As expected, some other research revealed that MIT just plays a limited role, and its advantages should not be overestimated. By monitoring the left ventricular mechanics of 86 AML patients and data analysis, shaikh *et al.* [27] found that high-dose MIT therapy was associated with an excellent remission rate but with a significantly increased risk of clinical and subclinical early cardiotoxicity and heart failure. It happened that there was a similar case, Anderson *et al.* [28] analyzed data from a total of 328 patients from 66 institutions over a 4-year period. The results showed that CR rates in patients treated with ME (mitoxantrone, etoposide) and AD (cytarabine, daunorubicin) were 34% and 43%, respectively. Independent prognostic analysis found that patients treated with ME induction regimen had poorer survival performance than those treated with AD regimen and this fact indicated that AD regimen cannot be rudely replaced by ME regimen. In another study by Rowe *et al.* [29], three hundred and sixty-two older adults with previously untreated AML were randomized to a subgroup of daunorubicin, idarubicin or mitoxantrone with a standard dose of cytarabine.

3. Nanomedicine

Liposomes, discovered in the 1960s by Dr. Alec D. Bangham, have been investigated

Table 1. Part of favorable research about mitoxantrone.

Reference	No. of patients	Dose (mg/m^2)	CR rates (number)	Drug-related death rates (number)	Characteristics of AML patients	Time range
Sarah M. Larson [21]	78	ARA 3 g/m^2 daily for 2 days, MXR 60 mg/m^2 daily for 2 days	45% (35)	9% (7)	High-risk	2001.5-2008.7
Marconi *et al.* [24]	55	MEC-6/5/4 for 1 or 2 course(s)	45.4% (25)[1] in the 1st course	7.3% (4)	R/R	2009.1-2018.6
Franco Mandelli *et al.* [25]	2157	Cytarabine 25 mg/m^2 immediately followed by 100 mg/m^2 daily for 10 days plus etoposide 100 mg/m^2 daily for 5 days plus DNR 50 mg/m^2 or MXR 12 mg/m^2 or IDA 10 mg/m^2 daily on days 1, 3, 5.	DNR 68.7% (495/721), MXR 69.8% (502/719), IDA 66.9% (480/717)	DNR 8.9% (64), MXR 10.0% (72), IDA 10.3% (74)	NA	1993.11-1999.12
Löwenberg *et al.* [23]	489	DNR 30 mg/m^2 daily for 3 days or MTZ 8 mg/m^2 daily for 3 days, both plus ARA 100 mg/m^2 daily for 7 days (repeat in two cycles), followed by low-dose ARA 10 mg/m^2 daily	MTZ 46.6% (115/247), DNR 38% (92/242)	MTZ 21.1% (52/247), DNR 14.9% (36/242)	Elder people (median age of 68 years)	1986.4-1993.11

Abbreviations: CR, complete remission; ARA, cytarabine; MXR, MTZ, mitoxantrone; MEC-6, mitoxantrone 6 mg/m^2, etoposide 100 mg/m^2, cytarabine 1 g/m^2 daily for day 1 to day 6; MEC-5/4, same daily doses than MEC-6 but administered in a 5/4-day schedule; R/R, relapse or resistant to conventional chemotherapy; DNR, daunorubicin; IDA, idarubicin.

in several pharmaceutical research as drug delivery systems [30]. By reason of the pharmacokinetics and pharmacodynamics alternations, the encapsulation of drugs inside liposomes improves their therapeutic effect [31]. Exploitation of the enhanced permeability and retention (EPR) effect via administer of nanoconstructs has been shown to consistently increase the fraction of the injected drug dose that reaches the tumor tissue. In further explanation of that, pathological tissue possessing more extravasation and deposition of macromolecular constructs thanks to larger fenestrations between the endothelial cells and thereby reduces the level of systemic side effects [32] [33]. Obviously, the benefits of these researches are seen in Doxil®, a liposomal formulation of doxorubicin [34]. Subsequently, CPX-351, a dual-drug liposomal encapsulation of cytarabine and daunorubicin at a fixed 5:1 ratio, were recently approved by the US Food and Drug Administration (FDA) for the treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes [35]. Despite most research concentrated on liposomal doxorubicin and daunorubicin, there were still several reports about Lipo-MIT. Li *et al.* [36] encapsulated mitoxantrone into 60, 80 and 100 nm pegylated lipid vesicles and discovered that the pegylated liposomal MIT (plm60) administered in KM mice showed at least 2 to 3 fold less toxic than free mitoxantrone (f-M). In L1210 ascitic tumor model, the

accumulation of plm60 in almost all normal tissues markedly decreased but increased in tumor zone conversely. Correspondingly, the half-life of plm60 was also considerably increased, with a $t_{1/2}$ of 16.2 - 19.0 h. This research certificated that plm60 was the most valid dosage displaying a longest survival time compared with plm80, plm100 and f-M. Meanwhile, antitumor efficacy of plm60 was beyond f-M in vitro. Furthermore, the superior anticancer effect of liposomal MIT than MIT and its dose-dependent activity saturation effect were mentioned in a related article [37]. A dose-escalating phase Ⅰ clinical trial of pegylated liposomal mitoxantrone and conventional mitoxantrone injection (c-MI) was designed to estimate safety and pharmacokinetics of plm60 [38]. Twenty patients of various tumors were enrolled in this study. Only mild hematologic toxicities were observed after plm60 injection at a dose of 10 mg/m^2. The toxicities induced by plm60 at this dosage were less than c-MI. Two CR and one PR (partial response) observed in non-Hodgkin's lymphoma patients might remind of the clue to potential efficacy. All three patients in c-MI group had stable disease. Lipo-MIT was also applied in other fields, such as advanced breast cancer, though there was no difference observed in ORR between two arms [19]. Compared with MIT, Lipo-MIT showed a lower incidence of cardiovascular events and myelosuppression, but higher incidence of anemia, skin hyperpigmentation and fever. Lipo-MIT provided a different toxicity profile, which might be associated with the altered distribution of the drug.

4. Conclusion

Though there were many treatment schedules including MIT, research yielded separate conclusions. Some studies supported the efficacy of MIT, while others had opposite results. Controversial efficacy of MIT compared to doxorubicin is existing. We believe the comparison of this drug in different studies indicated that a drug with a similar structure seems to be able to play a limited role in improving the effect, and we must be cautious about the difference in experimental results in different institutions. Liposomes are a promising evolutionary direction that provides higher drug dosage, lower toxicity, and better antitumor effect. Favorable research is limited to Lipo-MIT in leukemia cells *in vivo*. More clinical trials are needed to estimate feasibility of Lipo-MIT in AML patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Döhner, H., Weisdorf, D.J. and Bloomfield, C.D. (2015) Acute Myeloid Leukemia. *The New England Journal of Medicine*, **373**, 1136-1152. https://doi.org/10.1056/NEJMra1406184

[2] Evison, B.J., Sleebs, B.E., Watson, K.G., *et al.* (2016) Mitoxantrone, More than Just Another Topoisomerase II Poison. *Medicinal Research Reviews*, **36**, 248-299.

[3] Dimarco, A., Gaetani, M., Orezzi, P., *et al.* (1964) "Daunomycin", a New Antibiotic of the Rhodomycin Group. *Nature*, **201**, 706-707. https://doi.org/10.1038/201706a0

[4] Tan, C., Tasaka, H., Yu, K.P., *et al.* (1967) Daunomycin, an Antitumor Antibiotic, in the Treatment of Neoplastic Disease. Clinical Evaluation with Special Reference to Childhood Leukemia. *Cancer*, **20**, 333-353. https://doi.org/10.1002/1097-0142(1967)20:3<333::AID-CNCR2820200302>3.0.CO;2-K

[5] Arcamone, F., Cassinelli, G., *et al.* (1969) Adriamycin, 14-Hydroxydaimomycin, a New Antitumor Antibiotic from *S. peucetius var. caesius*. *Biotechnology and Bioengineering*, **11**, 1101-1110. https://doi.org/10.1002/bit.260110607

[6] Bonadonna, G., Monfardini, S., De Lena, M., *et al.* (1970) Phase I and Preliminary Phase II Evaluation of Adriamycin (NSC 123127). *Cancer Research*, **30**, 2572-2582.

[7] Bonadonna, G., Monfardini, S., De Lena, M. and Fossati-Bellani, F. (1969) Clinical Evaluation of Adriamycin, a New Antitumour Antibiotic. *British Medical Journal*, **3**, 503-506. https://doi.org/10.1136/bmj.3.5669.503

[8] Swain, S.M., Whaley, F.S. and Ewer, M.S. (2003) Congestive Heart Failure in Patients Treated with Doxorubicin: A Retrospective Analysis of Three Trials. *Cancer*, **97**, 2869-2879.

[9] Von Hoff, D.D. (1979) Risk Factors for Doxorubicin-lnduced Congestive Heart Failure. *Annals of Internal Medicine*, **91**, 710. https://doi.org/10.7326/0003-4819-91-5-710

[10] Murdock, K.C., Child, R.G., Fabio, P.F. and Angier, R.B. (1979) Antitumor Agents. 1. 1,4-Bis[(aminoalkyl)amino]-9,10-anthracenediones. *Journal of Medicinal Chemistry*, **22**, 1024-1030.

[11] Morley, J.O. and Furlong, P.J. (2006) Synthesis and Calculated Properties of Some 1,4-Bis(amino)anthracene-9,10-diones. *Organic & Biomolecular Chemistry*, **4**, 4005-4014. https://doi.org/10.1039/b610625k

[12] Shenkenberg, T.D. (1986) Mitoxantrone: A New Anticancer Drug with Significant Clinical Activity. *Annals of Internal Medicine*, **105**, 67. https://doi.org/10.7326/0003-4819-105-1-67

[13] Faulds, D., Balfour, J.A., Chrisp, P. and Langtry, H.D. (1991) A Review of Its Pharmacodynamic and Pharmacokinetic Properties.

[14] Walters, R.S., Kantarjian, H.M., Keating, M.J., *et al.* (1988) Mitoxantrone and High-Dose Cytosine Arabinoside in Refractory Acute Myelogenous Leukemia. *Cancer*, **62**, 677-682. https://doi.org/10.1002/1097-0142(19880815)62:4<677::AID-CNCR2820620405>3.0.CO;2-B

[15] Damiani, R.M., Moura, D.J., Viau, C.M., *et al.* (2016) Pathways of Cardiac Toxicity: Comparison between Chemotherapeutic Drugs Doxorubicin and Mitoxantrone. *Archives of Toxicology*, **90**, 2063-2076. https://doi.org/10.1007/s00204-016-1759-y

[16] Marzola, M., Parma, G., Bonazzi, C., *et al.* (1996) Salvage Therapy with Ifosfamide and Mitoxantrone in Advanced Ovarian Cancer. *Annals of Oncology*, **7**, 419-421. https://doi.org/10.1093/oxfordjournals.annonc.a010612

[17] Marriott, J.J., Miyasaki, J.M., Gronseth, G. and O'Connor, P.W. (2010) Evidence Report: The Efficacy and Safety of Mitoxantrone (Novantrone) in the Treatment of Multiple Sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*, **74**, 1463-1470. https://doi.org/10.1212/WNL.0b013e3181dc1ae0

[18] Tannock, I.F., de Wit, R., Berry, W.R., *et al.* (2004) Docetaxel plus Prednisone or

Mitoxantrone plus Prednisone for Advanced Prostate Cancer. *The New England Journal of Medicine*, **351**, 1502-1512. https://doi.org/10.1056/NEJMoa040720

[19] Wang, L., Cao, J., Li, C., *et al.* (2022) Efficacy and Safety of Mitoxantrone Hydrochloride Liposome Injection in Chinese Patients with Advanced Breast Cancer: A Randomized, Open-Label, Active-Controlled, Single-Center, Phase II Clinical Trial. *Investigational New Drugs*, **40**, 330-339. https://doi.org/10.1007/s10637-021-01182-7

[20] Koc, Y., Oyan, B., Kars, A., *et al.* (2004) A Randomized Trial of Continuous Infusion versus Bolus Mitoxantrone in Combination with Cytarabine in Newly Diagnosed Patients with Acute Myeloblastic Leukemia. *Hematological Oncology*, **22**, 43-53. https://doi.org/10.1002/hon.726

[21] Larson, S.M., Campbell, N.P., Huo, D., *et al.* (2012) High Dose Cytarabine and Mitoxantrone: An Effective Induction Regimen for High-Risk Acute Myeloid Leukemia (AML). *Leukemia & Lymphoma*, **53**, 445-450. https://doi.org/10.3109/10428194.2011.621562

[22] Arlin, Z., Case, D.C., Moore, J., *et al.* (1990) Randomized Multicenter Trial of Cytosine Arabinoside with Mitoxantrone or Daunorubicin in Previously Untreated Adult Patients with Acute Nonlymphocytic Leukemia (ANLL). Lederle Cooperative Group. *Leukemia*, **4**, 177-183.

[23] Löwenberg, B., Suciu, S., Archimbaud, E., *et al.* (1998) Mitoxantrone versus Daunorubicin in Induction-Consolidation Chemotherapy—The Value of Low-Dose Cytarabine for Maintenance of Remission, and an Assessment of Prognostic Factors in Acute Myeloid Leukemia in the Elderly: Final Report. European Organization for the Research and Treatment of Cancer and the Dutch-Belgian Hemato-Oncology Cooperative Hovon Group. *Journal of Clinical Oncology*, **16**, 872-881. https://doi.org/10.1200/JCO.1998.16.3.872

[24] Marconi, G., Talami, A., Abbenante, M.C., *et al.* (2020) MEC (Mitoxantrone, Etoposide, and Cytarabine) Induces Complete Remission and Is an Effective Bridge to Transplant in Acute Myeloid Leukemia. *European Journal of Haematology*, **105**, 47-55. https://doi.org/10.1111/ejh.13406

[25] Mandelli, F., Vignetti, M., Suciu, S., *et al.* (2009) Daunorubicin versus Mitoxantrone versus Idarubicin as Induction and Consolidation Chemotherapy for Adults with Acute Myeloid Leukemia: The EORTC and GIMEMA Groups Study AML-10. *Journal of Clinical Oncology*, **27**, 5397-5403. https://doi.org/10.1200/JCO.2008.20.6490

[26] Deng, L., Zhang, C., Ying, S., *et al.* (2021) Effect of Dose Ratio on Mitoxantrone and Daunorubicin in Acute Myeloid Leukemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Lymphoma, Myeloma and Leukemia*, **21**, e10-e20. https://doi.org/10.1016/j.clml.2020.08.001

[27] Shaikh, A.Y., Suryadevara, S., Tripathi, A., *et al.* (2016) Mitoxantrone-Induced Cardiotoxicity in Acute Myeloid Leukemia—A Velocity Vector Imaging Analysis. *Echocardiography*, **33**, 1166-1177. https://doi.org/10.1111/echo.13245

[28] Anderson, J.E., Kopecky, K.J., Willman, C.L., *et al.* (2002) Outcome after Induction Chemotherapy for Older Patients with Acute Myeloid Leukemia Is Not Improved with Mitoxantrone and Etoposide Compared to Cytarabine and Daunorubicin: A Southwest Oncology Group Study. *Blood*, **100**, 3869-3876. https://doi.org/10.1182/blood-2001-12-0354

[29] Rowe, J.M., Neuberg, D., Friedenberg, W., *et al.* (2004) A Phase 3 Study of Three Induction Regimens and of Priming with GM-CSF in Older Adults with Acute Myeloid Leukemia: A Trial by the Eastern Cooperative Oncology Group. *Blood*, **103**, 479-485. https://doi.org/10.1182/blood-2003-05-1686

[30] Bangham, A.D. and Horne, R.W. (1964) Negative Staining of Phospholipids and Their Structural Modification by Surface-Active Agents as Observed in the Electron Microscope. *Journal of Molecular Biology*, **8**, 660-668. https://doi.org/10.1016/S0022-2836(64)80115-7

[31] Bulbake, U., Doppalapudi, S., Kommineni, N. and Khan, W. (2017) Liposomal Formulations in Clinical Use: An Updated Review. *Pharmaceutics*, **9**, 12. https://doi.org/10.3390/pharmaceutics9020012

[32] Hashizume, H., Baluk, P., Morikawa, S., *et al.* (2000) Openings between Defective Endothelial Cells Explain Tumor Vessel Leakiness. *The American Journal of Pathology*, **156**, 1363-1380. https://doi.org/10.1016/S0002-9440(10)65006-7

[33] Taurin, S., Nehoff, H. and Greish, K. (2012) Anticancer Nanomedicine and Tumor Vascular Permeability; Where Is the Missing Link? *Journal of Controlled Release*, **164**, 265-275. https://doi.org/10.1016/j.jconrel.2012.07.013

[34] Safra, T., Muggia, F., Jeffers, S., *et al.* (2000) Pegylated Liposomal Doxorubicin (Doxil, Reduced Clinical Cardiotoxicity in Patients Reaching or Exceeding Cumulative Doses of 500 mg/m^2. *Annals of Oncology*, **11**, 1029-1033. https://doi.org/10.1023/A:1008365716693

[35] Lancet, J.E., Uy, G.L., Cortes, J.E., *et al.* (2018) CPX-351 (Cytarabine and Daunorubicin) Liposome for Injection versus Conventional Cytarabine plus Daunorubicin in Older Patients with Newly Diagnosed Secondary Acute Myeloid Leukemia. *Journal of Clinical Oncology*, **36**, 2684-2692. https://doi.org/10.1200/JCO.2017.77.6112

[36] Li, C., Cui, J., Wang, C., *et al.* (2008) Encapsulation of Mitoxantrone into Pegylated SUVs Enhances Its Antineoplastic Efficacy. *European Journal of Pharmaceutics and Biopharmaceutics*, **70**, 657-665. https://doi.org/10.1016/j.ejpb.2008.05.019

[37] Li, C., Zhao, X., Deng, C., *et al.* (2014) Pegylated Liposomal Mitoxantrone Is More Therapeutically Active than Mitoxantrone in L1210 Ascitic Tumor and Exhibits Dose-Dependent Activity Saturation Effect. *International Journal of Pharmaceutics*, **460**, 165-172. https://doi.org/10.1016/j.ijpharm.2013.10.023

[38] Yang, J., Shi, Y., Li, C., *et al.* (2014) Phase I Clinical Trial of Pegylated Liposomal Mitoxantrone plm60-s: Pharmacokinetics, Toxicity and Preliminary Efficacy. *Cancer Chemotherapy and Pharmacology*, **74**, 637-646. https://doi.org/10.1007/s00280-014-2523-8