Article

Effectiveness of hepatoprotective medication during cancer chemotherapy

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Highlights

This is a retrospective study including a cohort of 98 cancer patients. We evaluated the effectiveness of three commonly used natural substances during chemotherapy for preventing liver damage. A significant hepatoprotective benefit of magnesium isoglycyrrhizinate for liver protection of cancer patients undergoing chemotherapy is highlighted.

Editor's Summary

Hepatoprotective substances substantially used in Chinese hospitals - GSH, PPC and MgIG - influenced enzymatic values differently. GSH and MgIG may be similarly effective in preserving liver function and preventing drug-induced liver damage in cancer patients undergoing chemotherapy. However, PPC may have no significant activity in protecting liver function.

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Abstract

Objective: Chemotherapy may cause drug-induced liver damage and studying the effectiveness of hepatoprotective substances in the clinical context is still warranted. We assessed the effectiveness of three commonly used natural substances for liver protection in East Asia. **Methods:** Retrospectively, we collected all medical records during a period of three years of cancer patients that underwent chemotherapy treatment and received glutathione, magnesium isoglicyrrhyzinate or polyene phosphatidylcholine at a Chinese integrative medicine hospital. Liver enzymes before and after one treatment cycle were detected. Paired t-test, chi-square, Snedcor's F distribution and ANOVA were used to analyze data. **Results:** 98 individuals were eligible for inclusion. After treatment, in the glutathione group, there were lower values in alanine aminotransferase ($P < 0.05$) and aspartate aminotransferase ($P < 0.05$). There was also a lower level of liver injury in patients ($P < 0.05$). In the magnesium isoglycyrrhizinate group there were lower values in total protein ($P < 0.05$), alkaline phosphatase ($P < 0.05$) and gamma glutamyl transpeptidase values ($P < 0.05$). There was also a lower level of liver injury in patients after treatment ($P < 0.05$). In the polyene phosphatidylcholine group, there were no lower values of interest, including those of liver injury in patients ($P > 0.05$). **Conclusion:** Glutathione and magnesium isoglicyrrhyzinate may be similarly effective in preserving liver function and preventing drug-induced liver injury in cancer patients undergoing chemotherapy. Polyene phosphatidylcholine may have no significant activity in protecting liver function and preventing drug-induced liver injury in advanced cancer patients undergoing chemotherapy. Since elevated glutathione levels may increase the antioxidant capacity and the resistance to oxidative stress by cancer cells, it is plausible to conclude that maintenance of high intracellular levels of glutathione could be critical for metastatic cells growth.

Keywords: Cancer, Chemotherapy, Hepatoprotective, Drug-induced liver injury, Magnesium Isoglycyrrhizinate, Glutathione, Phosphatidylcholine.

摘要

目的：化疗可能会引起药物性肝脏损害，因此有必要在临床中研究保肝药物的有效性。我们评估了东亚地区三种常用的天然物质对肝脏的保护作用。

方法：收集三年来在中国某中西医结合医院接受化疗治疗，同时接受谷胱甘肽，异甘草酸镁或多烯磷脂酰胆碱治疗的所有肿瘤患者信息。每个治疗周期前后分别检测各组肝酶水平。使用配对 t 检验，卡方检验，F 分布和方差分析来分析数据。

结果：98 例患者被纳入研究。治疗后，在谷胱甘肽组中，患者丙氨酸转氨酶（$P < 0.05$）和天冬氨酸转氨酶（$P < 0.05$）的水平降低；患者肝损伤相关指标水平也较低（$P < 0.05$）。在异甘草酸镁组中，患者总蛋白（$P < 0.05$），碱性磷酸酶（$P < 0.05$）和谷氨酰转肽酶值（$P < 0.05$）的水平降低；治疗后患者的肝损伤水平也较低（$P < 0.05$）。在多烯磷脂酰胆碱组中，没有发现研究指标的降低，患者的肝损伤也没有得到改善（$P > 0.05$）。

结论：在接受化疗的肿瘤患者中，谷胱甘肽和异甘草酸镁对保护肝功能和预防药物引起的肝损伤同样有效。在肿瘤进展期接受化疗的患者中，磷脂酰胆碱在保护肝功能和预防药物引起的肝损伤方面可能没有显著效果。

关键词：癌症；化疗；保肝；药物引起的肝损伤；异甘草酸镁；谷胱甘肽；磷脂酰胆碱

Abbreviations: DILI, Drug-induced liver injury; NCI，National Cancer Institute; CTCAE，Common Toxicity Criteria for Adverse Events; TP, Total protein; ALT, Alanine aminotransferase; AST, Aspartate transaminase; GGT, Gamma glutamyl transpeptidase; GSH, Glutathione; PPC, Polyene phosphatidylcholine; MgIG, Magnesium isoglicyrrhyzinate; TBIL, Total bilirubin; ALB, albumin.

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Background

Drug-induced hepatotoxicity prevention in clinical oncology is important because it is a common side effect of chemotherapy [1]. The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents. Drug-induced liver injury (DILI) refers to hepatotoxicity by medicinal agents. Special populations such as cancer patients are at increased risk of DILI [2]. It can span from asymptomatic elevation in transaminases to severe disease such as acute hepatitis leading to acute liver failure. Although total bilirubin levels, transaminase levels, serum alkaline phosphatase levels, and/or serum albumin levels are the most frequently utilized parameter to adjust chemotherapy dosing [3], reports of active management of liver injury related to chemotherapy are lacking in the literature [2,4]. The severity of cases of DILI can vary greatly, from mild, transient and asymptomatic elevations in serum enzyme levels to acute liver failure leading rapidly to death or need for liver transplantation. In assessing DILI, it is important to categorize severity in an objective manner. However, the variability in manifestations of drug-induced liver disease makes it difficult to use a single symptom, laboratory abnormality or outcome to grade the severity of injury [5]. The Cancer Therapy Evaluation Program of the National Cancer Institute (NCI) of the National Institutes of Health, created the Common Toxicity Criteria for Adverse Events (CTCAE), toxicity criteria for adverse events that include liver injury grading [6]. In this system, the following levels are used to assess severity, with the values expressed as multiples of the upper limit of the normal range (Table 1).

It is a common practice for oncologists in China to prescribe hepatoprotective medication concomitantly with chemotherapy. Herbal medicines are becoming popular worldwide, despite their mechanisms of action being generally unknown. According to Molassiotis *et al*. (2009), the vast majority of the studies have shown that Chinese medicinal herbs improved treatment side effects, quality of life, and performance status, and some have provided evidence of tumor regression and increased survival [7]. Although no clinical recommendations can derive from the majority of studies, due to low quality, the number of studies reporting positive results is high enough to suggest that Chinese medicinal herbs may have a role in cancer care.

Regarding effectiveness of Chinese medicine for liver protection and chemotherapy among cancer patient, Liu *et al*. (2011) confirmed that the use of Chinese herbal formulas with chemotherapy resulted in protection of the liver during chemotherapy, as manifested by lower serum AST and ALT levels [8].

Negative articles issuing warnings, uninformed and with poor supporting evidence regarding adverse interactions between herbs and chemotherapy have been published. Yet, Treasure (2005) found there was no single case report in the literature of any harmful interaction between a botanical and conventional antineoplastic treatment [9]. For both practitioners and cancer patients, the effect of negative articles is to create fear and may even warm patients away from asking their caretakers about integrative supportive treatment or disclosing non-conventional treatment they may be undertaking.

This study aimed to do a comparison of the three main hepatoprotective medications used - glutathione, polyene phosphatidylcholine and magnesium isoglycyrrhizinate - in patients treated at the oncology department of the Jiangsu Province Integrative Chinese and Western Medicine, located in Nanjing, PRC, and consider what might be the best hepatoprotective medication for preventing liver injury in cancer patients undergoing chemotherapy treatment.

Table 1 Liver injury grading proposed by CTCAE

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT	Normal	> 1.0-2.5	> 2.5-5.0	> 5.0-20	> 20
AST	Normal	> 1.0-2.5	> 2.5-5.0	> 5.0-20	> 20
ALP	Normal	> 1.0-2.5	> 2.5-5.0	> 5.0-20	> 20
GGT	Normal	> 1.0-2.5	> 2.5-5.0	> 5.0-20	> 20
Bilirubin	Normal	> 1.0-1.5	> 1.5-3.0	> 3.0-10	> 10

Methodology

A computerized search performed by the hospital's information management department for all cancer patients treated since the year 2010, the time the hospital began to use a computerized recording system.

Inclusion criteria

1. Male or female aged 18-80 years. 2. Patients with a cancer diagnosis, having undergone chemotherapeutic treatment. 3. Karnofsky Score ≥50. 4. Estimated life expectancy ≥ one month; 5. Not having undergone chemotherapy in the last 30 days; 6. Completion of one chemotherapy cycle, regarded as complete when it was not stopped or postponed, based on the recorded chemotherapy regimen.

Exclusion criteria:

1. Patients that took more than one hepatoprotective medication or natural products specifically for liver protection at the same time. 2. Know hypersensitivity to glycyrrhizin. 3. Use of any hepatoprotectives in the previous 2 weeks. 4. Serious heart, liver or kidney disease, or metabolic disorder.

A structured questionnaire sheet to abstract data from patients' medical records was used (see supplementary documents). After data abstraction was completed, patient's names were replaced by coded numbers to ensure anonymity. The study was approved by the hospital's administration in October 2013. Subjects' written consent was not required, since patient identifiers were not included in the data.

Participants

All subjects had a cancer diagnosis and had been treated with chemotherapy at the Jiangsu Province Integrative Medicine Hospital in Nanjing from January 2010 to October 2013. This hospital offers both conventional and Chinese medicine healthcare services. All eligible patients were included. A total of 800 patients with cancer were identified from medical records provided by the hospital's Information Management Department and their data were analyzed. Among the 800 subjects, 98 fitted inclusion criteria. No randomization was applied in the magnesium isoglicyrrhyzinate (MgIG) and polyene phosphatidylcholine (PPC) groups, all eligible subjects were included. As all patients received some sort of hepatoprotective, no control group was established. Unit of analysis was one completed course of chemotherapy. Chemotherapy protocols included are described in Table 2.

Table 2 Chemotherapy protocols

Treatment	Agents		
Single-agent chemotherapy	Carboplatin Cisplatin Docetaxel Raltitrexed	Irinotecan Oxaliplatin Pemetrexed	Vinorelbine Xeloda Epirubicin
Two-agents combination	Capecitabine + Taxol Oxaliplatin + Xeloda Gemcitabine + Oxaliplatin Cisplatin + Carboplatin Paclitaxel + Cisplatin Irinotecan + Capecitabine Docetaxel + Cisplatin Paclitaxel + Gemcitabine Irinotecan + Pemetrexed Docetaxel + Nedaplatin Pemetrexed + Carboplatin Navelbine + Carboplatin Epirubicin + Nedaplatin Pemetrexed + Xeloda	Gemcitabine + Cisplatin Carboplatin + Irinotecan Paclitaxel + Carboplatin Gimeracil / oteracil Docetaxel + Carboplatin Paclitaxel + Epirubicin Irinotecan + FU Docetaxel + Epirubicin Paclitaxel + Xeloda Lapatinib + Cisplatin Docetaxel + Xeloda Pemetrexed + Nedaplatin Oxaliplatin + Capecitabine Etoposide + Carboplatin	
Three-Agents	Oxaliplatin + Xeloda + Carboplatin		

Combination	Etoposide + Cisplatin + gimeracil / oteracil
	Xeloda + Paclitaxel + FOLFOX
	Carboplatin + Icotinib + Cisplatin
	Cisplatin + Epirubicin + Nedaplatin
	Ciclophosphamide + Epirubicin + Vincristine
	Docetaxel + Oxaliplatin + gimeracil/oteracil
	Ifosfamide + Epirubicin + Cisplatin

Hepatoprotective medication prescription

Intravenous glutathione (GSH) 120mg or 180mg, daily; intravenous PPC 465mg or 930mg IV daily; and intravenous MgIG 100mg or 150mg IV daily. This medication was prescribed for 15 days, in average, to all subjects.

Measurements

A structured questionnaire sheet was used to collect demographic data, including age, gender, diagnosis, cancer status, liver injury status, concomitant chronic diseases, chemotherapeutic agent and detailed liver function data before and after chemotherapy. Patients had blood tests for aspartate transaminase (AST), alanine aminotransferase (ALT), total protein (TP), total bilirubin (TBIL), gamma glutamyl transpeptidase (GGT) and albumin (ALB) just before the start of a course of chemotherapy and one month in average thereafter, following the hospital's protocol. The average time between blood tests was 20 days (P = 0.183).

Data Analysis

The Statistical Package for the Social Sciences (SPSS, version 21.0 for Windows, SPSS Inc, Chicago, IL) was used to perform the data analysis. Student's paired t-test, chi-square and ANOVA were used when deemed appropriate to analyze group differences and pre-post-treatment results. Parametric tests were applied, as each group had more than 30 subjects and a normal distribution. In all analyses, a 95% confidence interval was used.

Results

Patients' characteristics

98 individuals were eligible for inclusion. Although most patients' baseline characteristics were slightly significantly different (Table 3), the great majority was at a TNM stage IV (P = 0.013) and had no liver injury or grade I liver injury (P = 0.125). Chemotherapy used in each group is detailed in appendix Table 1. Except for Pemetrexed, all of the chemotherapeutic agents in this research had an inherent risk hepatotoxicity (see appendix Table 2). The starting time of chemotherapy and hepatoprotective medication had a two-day difference on average (sd = 6) (appendix Table 3).

Table 3 Baseline characteristics of participants (n = 98)

		GSH (n=31)	MgIG （n=31）	PPC (n=36）	*P*
Gender %	Male	35.5	67.7	55.6	0.119
	Female	64.5	28.3	44.4	
Age (years)	Lower limit	29	45	34	
	Upper limit	79	75	73	0.136
	Mean	62	60	59	
	Breast	16.1	16.1	5.6	

Type of Cancer %	Colon	9.7	9.7	13.9	
	Esophagus	19.4	3.2	2.8	
	Gall Bladder	3.2	3.2	5.6	
	Lung	6.5	35.5	36.1	0.207
	Ovarian	16.1	3.2	5.6	
	Rectum	6.5	16.1	5.6	
	Stomach	9.7	16.1	13.9	
	Other	12.9	12.9	11.1	
TNM %	I	0.0	3.2	0.0	
	II	6.5	3.2	0.0	0.013
	III	6.5	0.0	30.6	
	IV	61.3	67.7	69.4	
Liver Injury %	Unclear	25.8	25.8	0.0	0.125
	No injury	45.2	48.4	47.2	
	Grade 1	35.5	22.6	52.8	
	Grade 2	3.2	16.1	0.0	
	Grade 3	12.9	12.9	0.0	
	Grade 4	3.2	0.0	0.0	

GSH, Glutathione; MgIG, Magnesium isoglicyrrhyzinate; PPC, Polyene phosphatidylcholine.

Glutathione

In the GSH group, there were significantly lower values of total protein (P = 0.003), ALT (P = 0.040) and AST (P = 0.022) (Table 4). After treatment, there was also a lower level of liver injury in patients (P = 0.043) (Table 5).

Magnesium isoglycyrrhizinate

In the MgIG group, there were significantly lower values in total protein (P = 0.036), alkaline phosphatase (P = 0.026) and GGT values (P = 0.016) (Table 6). After treatment, there was also a lower level of liver injury in patients (P = 0.012) (Table 5).

Polyene phosphatidylcholine

In the PPC group, there were significantly lower values only in total protein (P = 0.036) (Table 7). After treatment, there was no significant lower level of liver injury in patients (P = 0.096) (Table 5).

Table 4 Comparative analysis of relevant markers before and after treatment in the GSH group

GSH			
		Mean	*P*
TP	pre	679.3	0.003
	post	642.1	
ALT	pre	295.8	0.040
	post	227.7	
AST	pre	426.5	0.022
	post	332.3	

GSH,Glutathione; TP, Total protein; ALT, Alanine aminotransferase; AST, Aspartate transaminase.

Table 5 Liver injury grading according to the CTCAE before and after treatment

Agents		***P***
GSH	pre	0.043
	post	
GGT	pre	0.012
	post	
MgIG	pre	0.096
	post	

GGT, Gamma Glutamyl transpeptidase; GSH, Glutathione; MgIG, Magnesium isoglicyrrhyzinate.

Table 6 Comparative analysis of relevant markers between pre- and post-treatment in the MgIG group

MgIG			
		mean	*P*
TP	pre	651.7	0.036
	post	621.7	
ALT	pre	1 964.5	0.026
	post	1 542.6	
GGT	pre	1 462.6	0.016
	post	992.6	

TP, Total protein; ALT, Alanine aminotransferase; GGT, Gamma Glutamyl transpeptidase; MgIG, Magnesium isoglicyrrhyzinate.

Table 7 Comparative analysis of relevant markers between pre- and post- treatment in the PPC group

PPC			
		mean	*P*
TP	pre	683.417	0.036
	post	655.889	

TP, Total protein; PPC, Polyene phosphatidylcholine.

Discussion

The importance of reducing dose-limiting toxicities was shown by Neugut *et al*. (2006) [10]. The rationale in the clinical setting is that significant reductions in toxicity may alleviate dose-limiting toxicities so that more patients are able to complete prescribed chemotherapy regimens and thus, in turn, improve the potential for success in terms of tumor response and survival. Block *et al*. (2007) performed a systematic review to consider the impact of antioxidant supplementation in combination with chemotherapy [11]. They provide suggestive evidence that antioxidant supplementation helps reduce some adverse reactions including neurotoxicity, thrombocytopenia, diarrhea, thus enabling increased or uninterrupted dosing in patients

who otherwise may discontinue treatment due to side effects.

Hepatoprotective substances aim at preventing liver cell necrosis, improving liver cell membrane stability and cell metabolism, and promoting regeneration of the liver [12]. Commonly used natural substances or derivatives in the West are glutathione, ursodeoxycholic acid or milk thistle extract. In the Peoples' Republic of China, glutathione is also used often, as well as glycyrrhizin or PPC. Due to their extensively different modes of action, the authors focus solely on elaborating those related to this study:

Glutathione is a naturally occurring nontoxic, tripeptide (glutamyl-cysteinyl-glycine) and is capable of preventing damage to important cellular components caused by reactive oxygen species such as free radicals, peroxides, lipid peroxides, and heavy metals [13]. It promotes expression of antioxidant genes and alterations of hepatocyte survival as well as the balance between necrotic versus apoptotic cell death [14]. Low glutathione is commonly observed in wasting diseases such as cancers [15]. Disturbances in GSH homeostasis have been associated with liver diseases induced by drugs and is considered relevant in treating hepatitis [16, 17].

PPC is a chemical contained in eggs, soybeans, mustard, sunflower and other foods. Animal research has indicated a significant positive effect in the prevention of lipid peroxidation and accelerating hepatic fibrosis regression [18]. Albeit low quality, two studies [19, 20] referring positive outcomes regarding DILI prevention in chemotherapy were found in the context of leukemia and breast cancer.

Glycyrrhizin is a triterpenoid saponin found in Glycyrrhiza glabra L. (Fabaceae) and is the chief sweet-tasting constituent of Glycyrrhiza glabra (liorice) root. Licorice is not traditionally used to specifically treat liver injury, other than for its use in detoxification in all sorts of poisoning but glycyrrhizin is used in Japan to reduce the risk of liver cancer in people with chronic hepatitis C and in China for protection of liver function and treatment of tumors [21-23]. MgIG is a third-generation formulation glycyrrhizin. Several publications cite MgIG's liver anti-inflammatory properties, including in cancer patients [24-28].

Significant reductions in toxicity may alleviate dose-limiting toxicities so that more patients are able to complete prescribed chemotherapy regimens and, in turn, improve the potential for success in terms of tumor response and survival. Specific antioxidant supplementation may help reduce some adverse reactions, enabling increased or uninterrupted dosing in patients who otherwise may discontinue treatment due to side effects. In this study, three hepatoprotective substances substantially used in Chinese hospitals - GSH, PPC and MgIG - influenced enzymatic values differently. MgIG was the substance that had a lower *P* value, both in liver enzymes reduction, as well as the liver injury score.

The lower total protein value after treatment in all three groups were most likely due to increased cell death resulting from chemotherapy and/or increased metabolic load as most subjects in the study were in TNM stage III or IV.

Oxidative stress is thought to be involved in the development of cancer in humans significantly [29], and the possible application of agents capable of modulating the oxidant-antioxidant balance in cancer treatment is of interest [30]. Yet, while GSH deficiency leads to an increased susceptibility to oxidative stress implicated in the progression of cancer, elevated GSH levels may increase the antioxidant capacity and the resistance to oxidative stress by cancer cells [31]. It is plausible that maintenance of high intracellular levels of GSH could be critical for the extravascular growth of metastatic cells [32]. On the other hand, magnesium isoglycyrrhizinate's radical scavenging abilities in biological systems are not clear [33]. They may play a role in the treatment of chronic liver diseases, but is certainly not a main mechanism. Instead, it inhibits an inflammatory response not only through oxidative damage inhibition, but also through the STAT3 pathway, inhibition of neutrophil cell infiltration [34], of release of TNf-a, inducible nitric oxide synthase, and of cyclooxygenase-2 mRNA expressions [35], as well as translocation of NF-kappaB into the nuclei, downregulation expression of MMP-9 [36], caspase-3 and inhibition of release of cytochrome C from mitochondria into the cytoplasm [37]. Thus we conclude that, in face of a risk of administering antioxidants to cancer patients, glycyrrhizin is a safer, and perhaps more effective option than glutathione.

Conclusion

GSH and MgIG may be similarly effective in preserving liver function and preventing drug-induced liver damage in cancer patients undergoing chemotherapy. Given concerns that elevated GSH levels may increase the antioxidant capacity and theus resistance to oxidative stress by cancer cells, MgIG may represent a potent drug, protecting the liver from injury incurred through chemotherapy-induced hepatotoxicity. PPC may have no significant activity in protecting liver function and preventing drug-induced liver damage in advanced cancer patients undergoing chemotherapy.

Conflict of interest

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