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A case of chemotherapy-induced congestive heart failure successfully treated with Chinese herbal medicine

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Summary
Objective: A case is presented to illustrate a potential effect of Chinese herbal medicine (CHM) formulas in treating chemotherapy-induced cardiotoxicity.
Clinical presentation: An 18-year-old adolescent male with refractory acute lymphoblastic leukemia (ALL) had experienced anthracycline-induced congestive heart failure (CHF) for 3 weeks. Under intensive care with conventional therapy, the patient still had exercise intolerance and depended on supplemental oxygen all day. Therefore, he consented to treatment with traditional Chinese medicine (TCM) for alternative therapy.
Interventions and outcomes: This patient was treated with modified Zhi Gan Cao Tang (ZGCT), three times a day for 2 months. After 6 days of CHM treatment, the patient could tolerate daily activity without supplemental oxygen. After 2 months of CHM treatment, the follow-up chest X-ray showed great improvements in pulmonary edema and cardiomegaly.
Conclusions: In this case, anthracycline-induced cardiotoxicity resolved slowly following the administration of modified ZGCT. It is suggested that the CHM formula has a protective effect on the progression of CHF secondary to the use of anthracyclines in pediatric cancer. Further studies to determine the mechanism and clinical trials are warranted.

Introduction

Several antineoplastic drugs in clinical use are known to induce cardiac side effects. These effects encompass a wide variety of clinic-pathologic syndromes with minor to severe clinical consequences.[1] Anthracycline is emerging as an active treatment against acute lymphoblastic leukemia (ALL). The antitumor activity of this agent is based on

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interactions with nuclear components, especially DNA and type II topoisomerases; however, the drug may also inhibit DNA and RNA synthesis.[2] Clinical studies have demonstrated that high doses of anthracyclines can prolong the 5-year event-free survival rate in patients with high-risk ALL,[3] but the dose-limiting cardiotoxic effects make the disease prognosis poor and can be fatal.

Each one of these anthracyclines has been implicated in the development of cardiac toxicity leading to cardiomyopathy and congestive heart failure. The side effects may be caused by the activation of apoptotic mechanisms of cardiomyocytes during therapy, resulting in reduced LV systolic performance.[4] Doxorubicin, a daunorubicin analog, has been reported to produce acute and self-limiting cardiomyopathy within 2—3 days of its administration. In a few cases, it has been connected to life-threatening cardiogenic complications at cumulative doses of 500—550 mg/m^2. Other risk factors for anthracycline-induced cardiotoxicity include high dose intensity, younger and older age at diagnosis, radiotherapy, combination therapy with other cardiotoxic chemotherapy, and longer length of follow-up.[5,6] Concurrent therapies that protect against anthracycline-induced cardiomyopathy, such as probucol, carvedilol, dexrazoxane, and antioxidant nutrients, have been proposed.[7] However, no effective and clinically applicable preventive treatment has yet been widely adopted.

Herein we report a case of severe cardiac toxicity in conjunction with the administration of doxorubicin plus FLAG regimes (fludarabine, cytarabine, and granulocyte colony-stimulating factor (G-CSF) support), successfully treated with Chinese herbal medicine (CHM) over a 2-month follow-up period.

Case report

An 18-year-old adolescent with relapsed ALL was admitted to the pediatric intensive care unit (PICU) with a 5-day history of severe dyspnea during 21 days of administration of the last dose with doxorubicin plus FLAG regimes. He had been diagnosed 4 years earlier as T-cell ALL- L1 morphology in the very high risk (VHR) classification, according to the protocol of the Taiwan Pediatric Oncology Group (TPOG)-ALL-2002, and was given complete chemotherapy.[8] One year later, he relapsed with pancytopenia and increased blast cells in the peripheral blood smear examination, and received induction, consolidation, first maintenance, and subsequent maintenance therapy according to the Memorial Sloan-Kettering-New York 2 (MSK-NY 2) protocol,[9] which resulted in partial response of the disease. He had had previous progression 4 months prior to this admission, at which time he was offered one cycle of chemotherapy with doxorubicin plus FLAG regimens for refractory ALL from August 25 to 30, 2012.[10] Treatment consisted of 50 mg/m^2 i.v. doxorubicin on days 1, 3, and 5, plus fludarabine 30 mg/m^2 and cytarabine 2000 mg/m^2 on days 1—5. Antiallergic medication was given with each cytarabine administration, which consisted of methylprednisolone 40 mg administered once a day from day −1 to day 5. During the interim cycle, he developed a grade-4 granulocytopenia. Treatment continued with a 20% dose reduction of fludarabine on day 2, and addition of G-CSF from day 2 to day 5. The patient received one complete cycle of treatment, but complained of delicate symptoms such as cough, slight chest discomfort, and a low grade fever the third week after this chemotherapy course.

On September 21, he started complaining of a dry debilitating cough and dyspnea that gradually got worse. He was markedly hypoxemic, with resting arterial blood gases at room air, pO_2 39.8 mm Hg, pCO_2 66.1 mm Hg, pH 7.36, bicarbonate 36.5 mmol/L, and oxygen saturation 64%. A chest radiograph compared to pre-chemotherapy therapy revealed diffuse alveolar opacities with perihilar consolidations, pleural fluid, and an enlarged cardiac silhouette. An electrocardiogram revealed sinus tachycardia with rare ventricular premature depolarizations, and portable echocardiography detected left ventricular dysfunction with ejection fraction (EF) <40%. He was briefly treated on supplemental oxygen via bi-level positive airway pressure (Bi-PAP), diuretic infusion, vasodilators, and inotropes with an initial clinical diagnosis of congestive heart failure (CHF). Empiric antibiotics were also prescribed for possible common or opportunistic infections. Due to the symptoms and chest plain film persisting, he consented and began to treatment with traditional Chinese medicine (TCM) on October 12, 2012.

On TCM observation, he was very fragile, perspiring, and dyspneic at rest. His temperature was 36.1 °C, arterial blood pressure 128/69 mm Hg, respiratory rate 40/min, and pulse rate 110/min. He had widespread inspiratory crackles on auscultation and signs of heart failure such as raised venous pressure or peripheral edema. The oxygen saturation was 96% under supplemental oxygen 30% via a Venturi facemask. His hemoglobin was 8.5 g/dl, WBC $4 \times 10^3/\mu L$ (88% neutrophils), and platelets $4 \times 10^3/\mu L$. Biochemical analyses showed AST and ALT were twice the upper limits and revealed an increase in total bilirubin. The patient had burnt black and chapped skin and lips. Tongue diagnosis revealed a rag texture, purple-redness, dryness, and peeled-liking coating. A TCM diagnosis of a deficiency of Heart-yin and -yang, accompanied by Heat entering nutrient-blood, were concluded. The prescription of TCM herbal formulas included ingredients (Table 1) administered daily in three separate doses. The herbal formulas used were all prepared and extracted using standard procedures of the Taiwan Good Manufacturing Practice (GMP) by the certified company Sun Ten Pharmaceutical Co., Ltd. (Taiwan). A rapid response to the TCM treatment allowed the removal of supplemental oxygen for hours. Clinical improvement was evident after 6 days of treatment; after 12 days of treatment, he needed no oxygen at rest and diuretics could be tapered off. His repeated chest plain film study on October 20, 2012, disclosed a slowly resolving pulmonary venous congestion. Upon discharge, after 18 days of TCM treatment, he was in good clinical condition with oxygen saturation 98% via pulse oximetry.

The patient returned to TCM clinics every two weeks for follow-up and received continuous CHM treatment until December 2012. His subsequent chest plain film studies indicated no sign of recurrence of pulmonary edema and cardiomegaly. The EF has risen to 55% that indicated previous cardiac damage. The series of chest X-ray, clinical