Delayed anthracycline-induced cardiomyopathy – case report

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ABSTRACT

A 43-year-old man was admitted to the hematology department due to second recurrence of anaplastic lymphoma T-cell ALK+. Lymphoma was diagnosed 28 years earlier. The patient received COP regimen (17 cycles) and CHOP (5 cycles), radiotherapy and underwent splenectomy. He achieved complete remission at that time. Relapse of the disease was diagnosed 8 years later, which was treated with 6 cycles of chemotherapy (cytarabine, mitoxantrone, vepeside and glucocorticoids) and high-dose chemotherapy followed by hematopoietic stem cell transplantation. Second disease recurrence was found in 2013, it was anaplastic lymphoma T-cell ALK+ stage IIA by Ann Arbor. Echocardiography and myocardial perfusion scintigraphy revealed chronic heart failure NYHA class I. Angiotensin receptor antagonist (ramipril) and β-blocker (carvedilol) were recommended. The patient underwent 6 cycles of ESHAP, complete remission was reported after the second cycle. High-dose therapy with autologous stem cell rescue was considered at that time. However, having T-cell ALK+ lymphoma with a relatively good prognosis, previous prolonged complete remissions (respectively – 12 and 8 years), an insufficient yield from the harvest ($3{,}33 \times 10^6$/kg CD34+ cells), heart failure and chronic active viral hepatitis B, the high risk intensive chemotherapy followed by hematopoietic stem cells transplantation was discontinued. The chemotherapy was complicated by brachial vein and superficial vein thrombosis of left upper limb and hypogammaglobulinemia. Follow-up echocardiography performed after completion of chemotherapy showed improvement in EF (64%).

KEY WORDS: anthracyclines, cardiomyopathy, case report

43-year-old patient with anaplastic T-cell ALK+ (anaplastic lymphoma kinase) and chronic active hepatitis B (HBV t. B) was admitted to the hematology department for chemotherapy treatment of second recurrence of lymphoma. The disease was diagnosed 28 years ago, first line chemotherapy was given – COP regimen (cyclophosphamide, vincristine, prednisone; 17 cycles). As the patient did not achieve complete remission (CR, complete response), he underwent further second line treatment – 5 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with subsequent radiotherapy (no medical documentation regarding the dose of radiation). Due to persistent splenomegaly, splenectomy was done afterwards. Complete remission of lymphoma was confirmed according to the diagnostic criteria. Left axillary lymphadenopathy and hypercalcemia were found 8 years after completion of second line treatment. Histopathology confirmed recurrence of T-cell anaplastic lymphoma. The patient underwent 6 cycles of chemotherapy with cytosine arabinoside, mitoxantrone, etoposide and corticosteroid. Subsequently he received a high-dose chemotherapy followed by autologous hematopoietic cells transplantation (auto-SCT, autologous stem cells transplantation). The conditioning chemotherapy was a combination of cyclophosphamide, with etoposide and carmustine. Re-staging scans and tests evaluating efficacy of the treatment confirmed complete remission of lymphoma.

Left axillary and supraclavicular lymphadenopathy was detected in 2013. PET-CT showed avid left axillary and left supraclavicular lymph nodes (SUV max 3.3), histology of axillary lymph node was consistent with T-cell ALK+ anaplastic lymphoma infiltration. After complete staging work-up final diagnosis of anaplastic lymphoma T-cell ALK+, IIA stage according to Ann Arbour was established. Echocardiography (ECHO) showed left ventricular dysfunction and ejection fraction (EF) 47%. Furthermore, SPECT-GATED myocardial perfusion was performed in order to evaluate left ventricle perfusion. It showed irregular perfusion of the left ventricle (LK) at rest with impairment of perfusion in the inferior wall, inferior-lateral and lateral along with mildly decreased perfusion in the anterior-septal wall. LV cardiac ejection fraction by technique GATED-SPECT rated at 36%. The cardiac failure NYHA class I was diagnosed and the patient started treatment with the angiotensin receptor antagonist (ramipril) and β-blocker (carvedilol).

Having abnormalities shown on imaging of heart (EF 36%), clinical symptoms of mild heart failure along with absence of risk factors for heart disease and normal echocardiography performed at the time of diagnosis of lymphoma, prior chemotherapy was most likely the cause of cardiomyopathy, as total administered dose of doxorubicin was 200 mg/m^2 and mitoxantrone 120 mg/m^2. Therefore, ESHAP protocol (etoposide, cisplatin, high dose of cytosine arabinoside, methylprednisolone) was recommended for the patient. Complete remission was achieved after 2 cycles. The patient received 6 cycles of ESHAP in total. He was not a candidate for high-dose chemotherapy followed by allogenic stem cell transplantation due to chronic active hepatitis B. After the second cycle of chemotherapy (when CR was confirmed) patient underwent mobilization of hematopoietic cells by cytosine arabinoside in combination with dexamethasone followed by granulocyte-colony stimulating factor (G-CSF). Total yield was 3.33×10^6 CD34+ cells/kg/cm^3.

The patient was treated with biphosphonates for hypercalcemia secondary to increased level of parathyroid hormone due to paraneoplastic syndrome (parathyroid gland abnormalities were excluded by scintigrafy) while being on chemotherapy ESHAP regimen. Of note, hypercalcemia was diagnosed at the time of both disease recurrences. During chemoteherapy the brachial vein thrombosis of brachial vein and superficial veins of the left upper limb were diagnosed, for which the patient received therapeutic dose of low molecular weight heparin treatment (dalteparin sulfate) at the beginning, after recanalization of veins confirmed by ultrasound doppler, a prophylactic dose was recommended. Intravenous infusion of immunoglobulins was used because of hypogammaglobulinemia found after completion of chemotherapy (ESHAP) (IgG level 411 mg/dl).

The echocardiography performed after the fifth cycle of chemotherapy according to ESHAP protocol showed a slightly enlarged left atrium (LA) and LV, slight reduction of the global systolic function with a small global hypokinesia walls LV, discrete relaxation disturbances of LV, and an increased EF to 50%. The patient was seen by cardiologist again before planned auto-SC to assess the risk associated with high-dose chemotherapy. Although, the patient did not have any clinical symptoms of heart failure, he was treated for it all the time (as above). In light of that high-dose chemotherapy followed by auto-SCT, would bring a high risk of worsening of heart failure. Follow up echocardiogram performed after the course of chemotherapy confirmed further increase in EF – up to 64%.

Having lymphoma with a favorable prognosis (anaplastic T-cell ALK+), the nature of recurrences (involved lymph nodes of left axilla and left supraclavicular fossa with no generalized lymphadenopathy or deterioration of PS, duration of the first and second CR – 12 and 8 years respectively), insufficient number of CD34+ cell recovery and high risk of exacerbation of heart failure after high-dose chemotherapy followed by auto-SCT along with chronic active hepatitis B, intensification of the treatment was abandoned. Recent PET CT performed after 7 months. Cu-

rrently, that is, seven months after the end of the chemotherapy, the CR still observed in the patient, was confirmed by successive computer tomography CT and PET/CT examinations.

COMMENTS

Chemotherapeutic agents, such as: antibiotics of the anthracycline class, high-dose cyclophosphamide, ifosfamide, and imatinib, have been associated with cardiotoxicity. Other agents that may induce a cardiac event include: 5-fluorouracil, cisplatin, interleukin-2. Moreover, etoposide, rituximab, alemtuzumab, paclitaxel may cause hypotension. Hypertension may be associated with cisplatin, bevacizumab, sorafenib and sunitinib [1].

High risk of heart failure is a major factor limiting application of the above-mentioned chemotherapeutic agents. This was confirmed in numerous clinical trials regarding treatment of haematological malignancies (including lymphoma) with gold standard – CHOP regimen based on anthracycline antibiotic. For instance, in a retrospective analysis of 135 patients with aggressive non-Hodgkin's lymphoma CHOP regimen was used as a first line chemotherapy. 27 (20%) patients developed cardiomyopathy within one year after the beginning of treatment, half of them were symptomatic for heart failure. Two independent risk factors of cardiac toxicity were identified in multivariate analysis: cumulative doxorubicin dose of 200 mg/m^2, above which 27% of patients had features of cardiomyopathy and the age over 50 (risk of heart damage was beyond 33% above mentioned cumulative dose) [2].

In a retrospective analysis 9438 patients were identified as patients with diffuse large cell B, 42% of the patients were treated with chemotherapy regimens based on anthracycline antibiotic. 29% risk of heart failure beside the higher efficacy was reported in this group [3].

Delay cardiotoxicity seems to be still underestimated. Among 1474 patients with Hodgkin's lymphoma cardiac function failure (n = 73) was reported as a third cause of death, after the secondary neoplasms (n = 137) and recurrent Hodgkin's lymphoma (n = 135) [4].

Our patient was diagnosed with cardiomyopathy 26 years after the initial treatment of lymphoma; it confirms the observations from randomized clinical trials. Furthermore, the rate of patients with impaired systolic function raised as time went on and doubled after 10 years, while in patients with mild, moderate and severe impairment function of LV, the rate was doubled after 5 years [5]. This may explain an absence of any heart failure symptoms at the time of first recurrence of lymphoma in our patient.

Depending on doses of cytostatics drugs, cardiotoxicity as a side effect is observed in 3–5% of patients after 5 years, the rate rises to 15% after 10 years post treatment [6]. Chemotherapy related cardiomyopathy is associated with a particularly poor prognosis, and its clinical course is worse comparing to idiopathic or ischemic cardiomyopathy [7].

Apart from that cardiotoxicity affects efficacy of anti-cancer therapy and quality of life of treated patients; it significantly increases risk of cardiac death. The problem of cardiotoxicity seems to be even more important, because the vast majority of patients eligible for chemotherapy with potentially cardiotoxic drugs have risk factors for cardiovascular disease (age, obesity, hypertension, coronary heart disease, dyslipidemia and diabetes). These factors exacerbate possible side effects (including cardiotoxicity) of chemotherapy agents – including the anthracycline antibiotics and also glucocorticoids, which are the most common drugs used in treatment of hematological neoplasms. Glucocorticoids significantly affect blood pressure control and glucose level in the peripheral blood [1]. Having that data, an appropriate management includes not only treatment of the patients with myocardial damage, but also prophylactic cardioprotective treatment. For example, in a group of 90 patients, 36 with acute leukemia and 45 patients with other hematological malignancies, high-dose chemotherapy followed by auto-SCT was used. Patients were randomized to the cardioprotective treatment with enalapril or carvedilol, or to the control group. In the group of patients receiving the cardipotective treatment, the number of deaths and myocardial infarctions were significantly lower in comparison with the control group (6.7% vs 22%, p = 0.036) [8].

Moreover, in the analysis of 201 patients with iatrogenic impairment of systolic cardiac function (EF < 45%) (including 41 patients with lymphoma) who received cardioprotective therapy, two predictive factors of optimal treatment were found: cardiac heart failure class III and IV NYHA when cardiological treatment was started and the period of time from the completion of chemotherapy to the onset of heart failure treatment [9]. The same management – treatment with ACE inhibitors and β-blocker, was effective in our reported patient – gradual improvement in EF of 36% to 64% was achieved.

Heart failure may be a consequence of myocardial injury or impairment of its function as a side effect of chemotherapy. Anthracyclines are main cytostatics damaging myocardium. They inhibit topoisomerase III through DNA and RNA polymerases and damage cell membranes as a result of free radicals formation. Important is the dose (cumulative dose), and the time of an anthracycline antibiotic administration (delayed toxicity), as well as a progressive, irreversible heart damage.

A conventional anthracycline chemotherapeutic agent is very effective. It is part of many chemotherapy regimens used in the treatment of both solid tumors and blood neoplasms. A main factor limiting its application is irreversible damage of cardiac function, resulting from short half-life of the drug and the large volume of distribution (hence the low saturation of the tumor). In case of anthracycline antibiotics use, co-existing risk factors of heart failure (except for combination chemotherapy and cumulative dose) are also important. They include: prior or concomitant radiotherapy – as it was in the case described above, the age of the patient, previously diagnosed heart disease and hypertension [10].

Liposomal doxorubicin is composed of a double phospholipid membrane, which makes it more stable, it has longer half-life and a lower risk of side effects, including damage of the heart with preserved function of anti-tumor activity. This is possible due to abnormalities of the stucture of blood vessel walls in the tumor, which are not observed in normal tissues, such as myocardium and gastrointestinal tract. This allows to reduce the distribution of the drug to the above-mentioned organs and systems [11, 12]. On the other hand, pegylated liposomal doxorubicin is characterized by that the liposomes are covered with methoxypolyethylene glycol, which protects them against detection by the mononuclear phagocytic system and prolongs their half-life in the blood stream without necessity of higher concentration of therapeutic agent. This reduces risk of adverse events, including deterioration of cardiac function, resulting in the possibility of administration 50% more cycles of chemotherapy [13]. There are clinical trials confirming efficacy and safety of unpegylated liposomal doxorubicin in patients diagnosed with heart disease or previously treated with anthracycline antibiotics. In a study conducted by Rigacci et al., in the group of 21 patients with lymphoma (diffuse large B cell lymphoma, mantle cells lymphoma) classical doxorubicin was replaced by liposomal form. This treatment was well tolerated and effective. The response rate was 90% of patients with pre-existing heart disease or previously treated with chemotherapy regimens based on anthracycline antibiotic [14]. In the single-arm, multi-center phase 2 clinical trial, the efficacy of treatment of patients with diffuse large B-cell lymphoma including non-pegylated liposomal doxorubicin used as a part of the R-COMP regimen (rituximab, cyclophosphamide, non-pegylated liposomal doxorubicin, mitoxantrone, prednisone) was evaluated in a group of 75 elderly patients (median age: 72), 53% of patients had a history of cardiovascular event. The overall response rate (ORR) was 71%, 3-year overall survival (OS) 71%, and 3-year progression-free survival (PFS) – 69%. Meanwhile, the cardiac side effects were observed in 15 out of 75 patients (21%), including the third and fourth stage of the CTCAE in 4% of patients [15]. The retrospective analysis of 37 patients with non-Hodgkin's lymphoma and concomitant heart disease or elderly patients – all with contraindications for classical doxorubicin, treated with chemotherapy regimens including unpegylated liposomal doxorubicin revealed that ORR was achieved in 80% of the patients with diffuse large cell B, and 89% of the patients with lymphoma T/NK, including CR in 75% and 55% of patients respectively [16]. Moreover, in patients with newly diagnosed non-Hodgkin's lymphoma (55 patients) high efficacy of chemotherapy based on unpegylated liposomal doxorubicin was confirmed; CR in 67.4%, and ORR in 82.6% [17]. Similarly, in a group of 80 patients (median age 70.9 years) suffering from high risk diffuse large B-cell lymphoma, efficacy of therapy based on unpegylated liposomal doxorubicin (R-COMP) was studied in comparison with the response obtained in all the patients. In the study group, 82.5% achieved CR and PR – 13.5% of patients [18]. The application of liposomal doxorubicin may be used as a primary prevention of the cardiac function damage apart from the secondary setting.

A new catalogue of chemotherapy issued in January 2014, and its attachment: C.21.b, describes in details the indications and contraindications for liposomal doxorubicin in presence of significant risk factors (such as coronary artery disease, mild systolic dysfunction, EF ratio 40–50%) in patients with non-Hodgkin's and Hodgkin's lymphomas (follicular lymphoma and diffuse B-cell large, peripheral and cutaneous T-cell lymphoma and other unspecified forms of lymphomas).

Currently, safer methods of blood neoplasms treatment are being made by means of introducing some new, safer cytostatics or using of targeted therapies, that is, not applying of chemotherapy protocols which contain cardiotoxic drugs.

In conclusion, prophylaxis of cardiotoxicity in patients with blood neoplasms includes assessment of risk factors for heart disease prior to the cytotoxic treatment, an appropriate stratification of patients for the treatment and cardioprotective management along with early detection of heart damage and optimal treatment of the cardiovascular system diseases.

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