Srce i krvni sudovi 2017; 36(S2): 62-64

Case Report

Non-Hodgkin lymphoma diffuse large B cell- Case report of therapy related cardiotoxicity with review of European Society of Cardiology Guidelines from 2016

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During the last few decades a great progress in treatment of Non-Hodgkin lymphoma (NHL) has been achieved. Irrespectively of clinical stage on disease presentation, in more than 50% of patients would be expected to live more than five years if they were diagnosed with one of the two commonest NHL subtypes, diffuse large B cell (DLBCL) and follicular lymphoma which together represent about 2/3 of all NHL patients[1-3]. Numerous clinical trials signifficantly contributed towards achieving these favorable treatment results by identifying R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) regimen as the "gold" standard of care1-3. Besides these two most frequent NHL subtypes, CHOP with or without rituximabom is also treatment of choice in most others, rare subtypes of NHL[4].

Contemporary recommendations for diagnosis and treatment of NHL very precisely define mandatory diagnostic procedures before, during and after treatment, as well as the approach which depends on clinical stage and the other important risk factors such as agse[4-6]. However, in spite of many decades ago observed potential cardiotoxicity of doxorubicin which is the backbone of CHOP chemotherapy, those recommendations do not provide accurate enough guidelines for initial cardiological assessment regarding the safety of doxorubicin administration, follow up after the treatment and possible prevention of cardiac damage. Still, contemporary recommendations for treatment of NHL define maimal doses and it is not supposed the cumulative dose of doxorubicin to be more than 400 mg/m^2.

In April 2016., a patient 64 years went to his regional hospital due to worsening of dry cough which has been present for one year and, the appearance of breathlessness and fatigue. On chest X-ray mediastinal tumor and right sided pleural effusion had been observed and the patient was referred for cardiac ultrasound (US) and chest CT scan. The cardiac US showed left vetricle (LV) of normal dimmensions, mild hypocontractile apical region of lateral and front wall, with ejekction fraction (EF) of 55%; mitral regurgitation 1+, pericardial effusion with 15 mm fibrin deposits arround right atrium and abnormal movement of free right atrial wall. On the MDCT scan emphisematous changes were found in lungs, as well as moderate right sided pleural effusion with compressive atelectasis of surrounding lung parenchyma, enlarged lymph nodes - in anterior mediastinum 18mm, paratracheal 12mm, subcarineal 30mm, pericardial 21mm, right hilar conglomerate lymph node mass 72x45mm, right tracheobronchial 35mm, in the hilum of the spleen conglomerate lymph node masses 57mm i 60x64mm, few single lymph nodes up to 24 mm. Lung function test revealed moderate pulmonary obstruction.

The patient had been referred to Clinic for Hematology of Clinical Centre of Serbia. On presentation no new complains except already mentioned, on physical examination no peripheral lymphadenopathy or hepatosplenomegaly, chest ausculatation revealed absent breath sound on the base of the right lung with normal cardiac findings. Laboratory investigations revealed normal full blood count, raised level of inflammatory markers with ESR 20 mm/1.h., CRP 6.8 mg/l, fibrinogen 4.3 g/l, and among the other findings elevated β2-microglobulin 3.33 mg/l, AST 86 U/l, ALT 144 U/l, LDH 382 U/l. ECG – no abnormal findings. Virology testing – HCV+. In 1985 he was treated due to pulmonary tuberculosis, since two and half years ago he has been treated for rheumatoid arthritis with methotrexate and prednisone, smoker 50 years. He had been referred for transbronchial needle biopsy of mediastinal tumor, afterwards on that specimen pathjologists diagnosed NHL DLBCL. Also, thoracocentesis had been performed with evacuation 1500 ml of serohemorrhagic fluid and afterwards the cytological findings were in line with primary diagnosis. No bone marrow infiltration was found on bone marrow biopsiy specimen.

The treattment had been commenced with CHOP regimen, and after obtaining consent from infectologist, he was subsequently treated with R-CHOP regimen. Following 1 cycle of CHOP and 3 cycles of R-CHOP with good tolerance without any complain and stable laboratory investigations including liver function tests, the interim CT scans had been performed on which were present mediastinal lymph nodes up to 10mm, in the hilum of the spleen 29x19mm, along greater curvature of stomach 25x23mm. Since the partial remission was achieved, for patient it was decided to receive additional four cycles of R-CHOP.

Five days after completion of eight cycle of R-CHOP the patient was admitted due to dry cough and fatigue.

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Physical examination findings were normal. Chest x-ray revealed shadow in basal parts of the right lung. Laboratory investtigations – except mild elevated transaminases there were also elevated ferritin 1546.2 ng/ml and, NTproBNP 7477 pg/ml. ECG – no abnormal findings. After commencement of antibiotics the patient had become better, he did not accept further examinations including cardiac US and he left the Clinic on third day.

Seven days after the discharge from the Clinic the cardiac US was performed and rexealed drop of LVEF on 40% with enargement of the LV. Two weeks after the discharge he was admitted in the Emergency Centre of Clinicial Centre of Serbia due to severe breathlesnsess, swelling of his legs and low urine output. On physical examination the chest auscultation revealed diminished breath sounds on the bases of both lungs along with inspiratory crackles, rhythmic cardiac activity, heart sounds diminished, mild apical and parasternal on left side systolic murmurs, hypotension 70/50 mmHg, HR 75/min, bilateral pretibial edema. ECG: sinus rhythm, reduced voltage in standard leads, incomplete right band branch block, micro s in D2, D3 and aVF, QS in V2-V3, negative T in V4-V6, s in D1. Laboratory investigations revealed BUN 11,2 mmol/l, creatinine 123 μmol/l, BNP 2694 pg/ml, hs troponine T 160 pg/ml, LDH 581 U/l, mild elevation of ttransaminases, CRP, D-dimer. The cardiac US visualised enlarged keft ventricle (6.7/6.3cm) globally hypocontractile, septum thin and akinetic as well as posterior wall, other parts hypokinetic, total LVEF 15%, no morphological changes on mitral valve, mitral regurgitation 3+, tricuspidal regurgitation 2-3+, enlarged right atrium, right ventricle enlarged 3.4cm. On chest X-ray findings were consistent with pneumonia, consolidated lung parenchyma in right middle and lower lung field and in left middle field, bilateral pleural effusion, size and shape of cardiac silhouette aorticomyopathic. After initial treatment the patient's condition was slightly improved, however on fifth day of hospitalization the patient complained on cough an severe breaathlessness, while prominent findings were orthodyspnea, cyanosis and auscultory findings consistent with pulmonary edema. Soon after that respiratory arrest occurred followed by heart rate decrease up to asystolia. The patient was rescued, intubated, supported by mechanical ventilation with restoring of spontaneus circulation but due to hypotension dual inotropic support was commenced. Next day after the cardiac arrest reoccurred the patient was again rescued with restored spontaneus circulation. Due to suspected pulmonary embolization on heart US and vital indication, the patient received thrombolytic therapy. Despite the treatment the patient remained hypotensive, anuric, in cardiogenic shock with signs of progressive multiorgan failure. Few hours afterwards the cardiac arrest reoccurred, but in spite of undertaken measures and prolonged resuscitation the spontaneus circulation was not restored, resulting in lethal outcome.

Discussion

Cardiac toxicity which is presented as heart failure after doxorubicin treatment represent rare, but potentially very severe treatment complication, since it can cause irreversible cardiac damage and has an impact on treatment outcome and prognosis[7]. The cardiotoxicity of anthracyclines may be acute, early or late[8-10]. Acute toxicity occurs in less than 1% of patients, immediately after infusion and it is usually transient, presented as supravetricular arrhythmia, left ventricle dysfunction, ECG changes. Early and late cardiotoxicity of antracyclines manifest themselves as heart failure with progressive decline of LVEF. Early toxicity occurs within first yerar after treatment, while late effects occur after several years.

In retrospective analysis in oncological trials, a dose dependent increase in incidence of anthracycline cardiotoxicity was observed[11]. Thus, after lifetime doxorubicine cumulative dose of 400 mg/m^2 the incidence of left ventricle dysfunction was up to 5%, while at cumulative dose of 700 mg/m^2 it may reach 48%. Beside that, the elderly patients were identified as vulnerable group since heart failure after treatment with anthracyclines occurs in up to 10% older than 65 years. Moreover, as risk factors for poor outcome were also identified pre-exising cardiac disease, hypertension, concomitant application of others potentially cardiotoxic chemotherapeutical drugs, anthracycline treatment in childhood[11-13]. Also, it was observed that early detection of decrease in LVEF and starting the treatment resulted in good functional recovery[14]. Hence, in contemporary clinical trials it remains a challenge to define optimal balance between treatment efficacy and potential treatment related toxicity, as well as optimal follow up algorithm. In that sense, the guidelines by European Society of Cardiology (ESC) represent an important step towards these aims[15].

Beside that in these guidelines by ESC Comittee for Practice Guidelines are defined risk factors as mentioned above, they also provide the recommendations for frequency of US assessments and further treatment based on these findings. Thus, in patients without risk factors and normal US findings with LVEF more than 50% before the treatment, it is recommended to perform US assessment after 200 mg/m^2 of doxorubicin, after completion of treatment, one year after and five years after the treatment. In patients with risk factors or decreased LVEF it is recommended to consider the possibility of omitting anthracyclines, the use of cardioprotective drugs, as well as more frequent US assessments. If there was a decrease in EF of 10% or more and the findings are in limits of normal, repeated assessment in short time during the treatment or immediately after is recommended. If the US findings are not within the limtis of normal, the commencement of treatment with ACE inhibitor (or angiotensin receptor blocker) combined with β-blocker if not contraindicated is recommended. This drug combination is given to patients with symptomatic heart failure or asymptomatic cardiac dysfunction. Measurement of at least one cardiac biomarker (high-sensitivity troponin I or T, or natriuretic peptide) may be considered before commencement of treatment, as well as measurement of troponin I with each cycle of therapy. Although so far it was not demonstrated that this strategy contribute in prevention or improvement of longer-term toxicity events, it can be useful

for identification of high risk patients who may benefit from preventive treatment. Still, it has to be pointed out that the way and frequency of follow up is defined by expert consensus based on retrospective data and this approach must be validated in prospective trials.

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