

Case report

Non-pegylated liposomal doxorubicin based on treatment of diffuse large B-cell lymphoma in old patient with increased cardiovascular risk – case report and review of literature

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ABSTRACT

The use of anthracyclines in the treatment of patients with diffuse large B-cell lymphoma is crucial, however may be sometimes difficult or even contraindicated due to coexisting cardiovascular diseases. An alternative to conventional anthracyclines seems to be liposomal forms that have been registered in the first line of treatment for women with metastatic breast cancer. Data on their use in patients with non-Hodgkin's lymphomas indicate high efficacy and acceptable toxicity. We present case report of treatment with immunochemotherapy using non-pegylated liposomal doxorubicin in elderly woman with diffuse large B-cell lymphoma coexisting with ischemic heart disease, hypertension, type 2 diabetes. In addition, we present review of literature and the aspects of the use of drugs off-label.

Key words: non-pegylated liposomal doxorubicin, cardiotoxicity, non-Hodgkin lymphoma

CASE REPORT

A female patient, aged 75, diagnosed with diffuse large B-cell lymphoma (DLBCL) was admitted to the Department of Hematology and Bone Marrow Transplant in Poznań, Poland, in January 2017. Since November 2016 she had complained about mandibular and ear pain on the right-hand side which was the reason she was referred by a primary care physician to the Out-patient Otorhinolaryngology Clinic of the Greater Poland Oncology Center. Magnetic resonance imaging (MRI) revealed a tumor with an obliterated outline in the right linguo-tonsillar sulcus and parapharyngeal space, with a significant contrast enhancement, measuring 30 × 24 × 40 mm in transverse view. The tumor infiltrated the medial wing muscle, extended posteriorly to the internal carotid artery and adhered to half of its circumference. On the right-hand side, rounded cervical lymph nodes were identified in region II and II/III, suspected of being invaded by the tumor and measuring, respectively, 14 × 12 mm and 10 × 8 mm. A sample has been obtained for testing. Based on an immunohistochemical study, the histological manifestation of the tumor was consistent with a high-grade B-cell lymphoma, most similar to a diffuse large B-cell lymphoma. The immunophenotype was determined as: LCA+, CD20+, BCL-2 inconclusive result, BCL-6+, CD10+, focal MUM1+, CD3-, D1Ck Ae1/Ae3 cyclin-, Ki-67 in nearly 90%. In addition, the patient suffered from ischemic heart disease CCS I, had a history of inferior wall infarction with ST-segment elevation in 2008, underwent angioplasty of right coronary artery involving stent implantation, as well as suffered from arterial hypertension, type 2 diabetes, lipid disorders and hypothyroidism. The following medications were used: 12.5 mg carvedilol, 50 µg levothyroxine, 850 mg metformin, 40 mg atorvastatin, 75 mg acetylsalicylic acid, 10 mg amlodipine and 10 mg ramipril.

Upon admission to the Hematology Clinic, the patient's overall health status was good but she complained of dysphagia. On physical examination, the patient's blood pressure was 130/80, and she had a regular heart rate of 80 beats per minute; no abnormalities were identified on cardiac and pulmonary auscultation, the abdomen was soft and painless, with no abnormal masses, the liver and spleen were not enlarged, and legs were not swollen. Abnormal findings included an enlarged right palatine tonsil and enlarged right cervical lymph nodes up to 2 cm.

The results of blood counts and blood chemistry tests were normal. An abnormality was detected in coagulation studies; the level of D-dimers was 1150 ng/ml (N < 500 ng/ml).

As the next available appointment for PET-CT scan was remote, computed tomography scans were performed as part of the in-

itial diagnostic process. A chest CT scan revealed minor fibrous degenerative changes in both lungs and a calcified primary complex in the right lung. Signs of osteoporosis, degenerative abnormalities in the thoracic spine, and a sclerotic island in Th5 vertebral body were noted. The thoracic aorta had calcifications in its wall.

Abnormal findings in the abdominal CT scan included a left kidney which was much smaller, 60 mm in length, hypoplastic, and with a small cyst measuring 5 mm. Cytological and cytometry studies of the bone marrow and trepanobiopsy revealed no signs of infiltration.

The patient was diagnosed with DLBCL, stage II E according to Lugano Classification.

ECG and echocardiogram were performed due to pre-existing cardiological conditions.

ECG showed a regular sinus rhythm of 82/min, and an intermediate heart axis. Non-pathological Q waves in III, aVF.

Echocardiogram: RV 25, IVS 10, LV 48, PW 8, Ao 32, LA 33, LVEF 55 (N > 50%), AcT of pulmonary aorta of 120 ms, E/A 70/100 cm/s (< 1), DecT 200 ms. Postcava – 1.3 cm in diameter, unobstructed, with a respiration-induced mobility. The pericardium showed no pathological volumes of liquid. Mitral valve – augmented cusps, minor regurgitation; aortic valve – augmented cusps, with calcifications and reduced mobility, Vmax 2.0 m/s; tricuspid valve – minor insufficiency; RVSP 30 mmHg; normal pulmonary valve. Left ventricular contractility – akinesis of the basal segment of inferior-posterior wall and interventricular septum. Conclusions: normal size of heart chambers. Sectional abnormalities in contractility were observed which were secondary to infarction of inferior-posterior wall, with a preserved systolic function. Impaired left ventricular relaxation. Combined benign aortic valve disease.

A cardiologist called for a consultation found no contraindications for anti-cancer treatment. He pointed out to a higher risk of cardiovascular complications.

A decision was made to initiate 6 cycles of R-COMP (rituximab 375 mg/m² i.v. once daily; cyclophosphamide, 750 mg/m² i.v. once daily; vincristine 1 mg/m² i.v. once daily; non-pegylated liposomal doxorubicin 50 mg/m² i.v. once daily; prednisone 100 mg on days 1 to 5).

The treatment was started on February 3th 2017. Following chemotherapy, the patient experienced cytopenia with a reduction in granulocyte count to 0.18 g/l and febrile neutropenia. In addition, anemia was diagnosed with HGB levels at 4.5 mmol/l. The patient required a transfusion of packed red blood cells. For those reasons, two subsequent cycles of chemotherapy were delayed. The patient received G-CSF and antibiotics. Partial remission was noted at the assessment after the 3th cycle of R-COMP. A follow-up echocardiography showed similar results on a range of parameters, with a slight decrease in left ventricular ejection fraction (LVEF) to 52%. No cardiovascular symptoms were observed. A decision was made to continue R-COMP therapy.

After the 5th cycle of chemotherapy, the patient was admitted to a local hospital due to fainting and pancytopenia. Acute coronary syndrome and focal abnormalities in the central nervous system were ruled out. In June 2017, the 6th cycle of R-COMP was administered, with cyclophosphamide and liposomal doxorubicin doses reduced by 50%.

After 6 cycles of R-COMP, an assessment was performed using PET-CT scan which found a complete metabolic remission, Deauville Scale 1. An echocardiogram of the heart performed in outpatient settings showed LVEF of 50%. The patient was referred for a follow-up to an outpatient hematology clinic. At 17 months from the completion of treatment, the patient has maintained a complete remission of the primary condition, is regularly followed-up by a cardiologist, and experiences no cardiovascular complications.

REVIEW OF RELEVANT LITERATURE

The median age of patients diagnosed with DLBCL is 65 years. Doxorubicin is an integral part of the R-CHOP regimen which is the recommended first line of treatment. However, due to cardiotoxicity of the conventional form of doxorubicin, the possibility to use it in patients with coexisting cardiovascular conditions, particularly elderly patients, is limited. Excluding doxorubicin from the armamentarium or reducing its dose adversely affects the efficacy of therapy which is particularly unfavorable in elderly patients; once resistance to treatment develops or the disease relapses, further treatment is difficult or impossible due to the patient's health status and coexisting conditions. A multi-center analysis of 610 patients with non-Hodgkin lymphomas (NHLs) of whom 581 received R-CHOP regimens, showed that cardiovascular complications were the second most frequent cause of mortality, responsible for 30% of all deaths [1]. A product with

non-pegylated liposomal doxorubicin (NPLD) as the active substance has been registered for use in combination with cyclophosphamide as the first line of treatment for adult female patients with metastatic breast cancer.

A number of studies on patients with NHLs receiving NPLD instead of conventional doxorubicin were performed. In each of the studies mentioned below, R-COMP immunochemotherapy was used.

The dose of NPLD used in patients with NHLs was determined on the basis of two studies comparing the efficacy and safety of therapies with doxorubicin in a dose of 40 mg/m², 50 mg/m², 60 mg/m² and 80 mg/m². One of the studies was conducted on patients with AIDS-related lymphomas [2] and the other on subjects with aggressive lymphomas [3]. In both studies, no dose-related toxicity was identified and both indicated a similar efficacy of the range of doses specified above. Based on those findings, a dose of 50 mg/m² was recommended to be used. The relevant literature also contains papers reporting on the use of doxorubicin at a dose of 40 mg/m².

A prospective phase II study was conducted at MD Anderson to review the toxicity of NPLD. The study group included 80 patients with DLBCL, with a median age of 69 years. With the exception of one patient, risk factors for cardiotoxicity were present in all subjects who underwent therapy with anthracyclines. ITT analysis demonstrated ORR of 86%, and CR of 78%. Cardiac adverse events more severe than grade 3 were identified in 3 patients (4%), which included one death due to heart failure. Cardiac adverse events of grade 1–2 primarily included asymptomatic decrease of ejection fraction, which was observed in 16 patients. Estimated 5-year EFS and 5-year OS were, respectively, 52% and 70% [4].

A study conducted by Dell'Olio et al. on 80 patients (median age of 70.9 years) achieved CR in 82.5% patients and PR in 13.7% patients. After a mean follow-up period of 31 months, 62 out of 80 patients (77.5%) have lived without signs of active disease, 3 out of 80 have lived with an active disease while 15 patients (18.7%) died. The estimated overall survival rates after 12 and 24 months from admission were 93.5 and 87.3%, respectively. No therapy-related cardiac events were identified, while ejection fraction improved (from 51.6 ± 6.9% to 54.2 ± 3.9%). Grade 3–4 neutropenia occurred in 22% subjects. The authors emphasize the high efficacy and good tolerance of the treatment, particularly in terms of its effect on the cardiovascular system [5].

It is also worth to report on a phase III randomized study conducted by the Austrian Cancer Drug Therapy Working Group which compared safety of R-COMP vs. R-CHOP in newly-diagnosed patients with DLBCL. Prior to each cycle and at the end of treatment, LVEF and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were assessed. Mean LVEF did not differ significantly between the two arms of the R-COMP vs. R-CHOP study ($p = 0.167$). During therapy, LVEF $< 50\%$ was significantly more frequent in patients treated with R-CHOP ($p < 0.001$). All results of NT-proBNP tests were consistently < 400 pg/ml ($p = 0.013$) in 36 out of 40 patients (90%) in the R-COMP arm but only in 24 out of 36 patients (66.7%) in the R-CHOP arm. More severe adverse events occurred in the R-CHOP arm (26 vs. 40; $p = 0.029$), including infections (15 vs. 28). The authors believe that a therapy consisting of 6 cycles of R-CHOP causes early cardiotoxicity to a little extent while NPLD does not lower cardiotoxicity significantly in patients with a normal heart function, however a higher level of markers of myocardial injury was observed during R-CHOP therapy [6].

In another study on 55 patients with DLBCL, troponin I (TnI) levels were measured prospectively and serial echocardiography studies were made to detect early signs of cardiotoxicity. The subgroup treated with NPLD had 39 patients, of whom 34 subjects were older than 65 years, showed a higher risk of cardiovascular complications and suffered from a greater number of co-existing conditions. Following treatment, results of echocardiography studies did not deteriorate in the NPLD group while 2 patients in the group receiving conventional doxorubicin had a significantly lower LVEF. TnI level showed a linear increase in the subgroup receiving conventional doxorubicin and a slight increase in the NPLD group. In case of doxorubicin dose > 200 mg/m², the difference in results was statistically significant. The NPLD subgroup did not experience a higher number of grade 3–4 adverse events. Both subgroups showed similar ORR and CR [7].

Among the literature discussing efficacy and toxicity of treatment with NPLD, particular attention should be paid to papers reporting on patients with coexisting cardiovascular diseases who received those medications. A retrospective analysis was performed on 25 patients with DLBCL whose median age was 73 years (range from 24 to 85 years). The majority of patients suffered from more than one cardiovascular disease, and 14 of them had a low LVEF. Each patient underwent 5 cycles of immunochemotherapy on average. After the treatment, ORR was 96% while CR and PR were, respectively, 44% and 52%. After a mean follow-up time of 23 months, 4 patients had a relapse. An estimated 3-year PFS was 66%, with 3-year OS of 73%. Car-

diac complications were the cause of death in 3 patients. After chemotherapy, median LVEF did not change significantly (51% vs. 50%). The group of patients who had a decreased LVEF prior to treatment did not experience any further lowering of LVEF after chemotherapy. Cardiac adverse events were observed in 36% patients, including two subjects who were diagnosed with a myocardial infarction. The authors believe that randomized studies need to be conducted in order to determine the safety profile [8].

In another study, a prospective analysis was performed on patients with aggressive NHLs and coexisting cardiovascular diseases or previously treated with anthracyclines. The study group included 21 patients and the treatment was continued until progression or until an unacceptable level of toxicity was reached. The following response rates were achieved: ORR of 90% and CR of 76%. Cardiac adverse events occurred in one patient. After a mean follow-up time of 13 months (2–36), 2 out of 16 patients who achieved CR experienced a relapse while the disease-free survival (DFS) was observed in 78% cases [9].

A report was published recently from a multi-center prospective phase 2 HEART01 study which assessed activity and efficacy of R-COMP. It included 50 patients with DLBCL and coexisting cardiovascular diseases. The median age was 76 years which is higher than the average age in DLBCL. Ischemic cardiomyopathy was the most frequent coexisting cardiovascular condition (35%) among the subjects, followed by permanent atrial fibrillation (15%), hypertrophy of left ventricle (13%) and initial LVEF $< 50\%$ (12%). ITT analysis showed ORR at 72%, including CR of 56% and PR of 16%. Grade 3–4 cardiac adverse events were observed in 6 patients. No significant deterioration of LVEF was identified in any of the subjects [10].

All the studies mentioned above lead to a conclusion that NPLD shows a high efficacy when used as a component of R-COMP immunotherapy with acceptable levels of toxicity in patients at a high risk of cardiovascular complications.

Among all the studies discussing different subgroups of patients with NHLs receiving NPLD, attention should also be paid to those which were conducted on elderly patients and patients not eligible for conventional R-CHOP chemotherapy.

Riciutti et al. retrospectively analyzed data on treatment of 29 patients over the age of 80 years (median age of 84 years) suffering from DLBCL or grade 3 B follicular lymphoma (FL). The patients were treated between January 2010 and August 2015.

The following survival rates were achieved: 3-year OS of 46%, 3-year cause-specific survival of 55% and 3-year PFS of 44%. When looking at the prognostic factors under review, only a complete remission strongly correlated with the survival rates mentioned above. No toxicity-related deaths occurred during therapy, and only mild symptoms were observed which did not require an admission to hospital. It seems that these optimistic results need to be construed with caution due to the retrospective nature of the study, small number of subjects in the group, and the probable preselection of patients who were included in the group [11].

Visani et al. conducted a prospective study of 20 patients with ill-health (median age of 73 years) suffering from DLBCL or 3 B FL. 45% of them had a performance status ≥ 2 as measured by the WHO scale. CR was achieved in 20 (65%) patients and PR was elicited in 5 (25%) subjects. After a mean follow-up time of 24 months, 15 out of 18 (83%) patients who showed CR have lived symptom-free and 3 out of 18 patients have survived with an active disease. In the course of treatment, patients primarily experienced hematological toxicity associated with grade $\frac{3}{4}$ neutropenia in 26% cycles and febrile neutropenia in 5% cycles. As for severe adverse events, 3 patients experienced WHO grade 3–4 incidents, including massive pulmonary embolism, congestive heart failure and, in one patient, ischemic heart failure. The authors conclude that R-COMP-21 is an efficacious regimen with promising response rates in elderly patients [12].

DISCUSSION

According to the position taken by Polish experts relating to the use of non-pegylated liposomal doxorubicin in patients with non-Hodgkin lymphomas and coexisting cardiovascular diseases, the indications for NPLD include: coronary heart disease, mild left ventricular systolic dysfunction with LVEF of 45–50%, insulin-dependent diabetes, chronic atrial fibrillation, ventricular arrhythmia, moderate aortic valve stenosis, complicated arterial hypertension, and a prior conventional doxorubicin therapy with a total dose of ≥ 200 mg/m². Anthracyclines in any form are believed to be contraindicated in advanced cardiovascular disease, including symptomatic heart failure of NYHA class III or IV, left ventricular systolic dysfunction with LVEF < 40%, prior heart infarction less than 6 weeks earlier, history of documented ventricular tachycardia, poorly controlled arterial hypertension and unstable angina pectoris (CCS III or IV class) [13]. Our patient achieved a complete metabolic remission after 6 cycles of R-COMP. Adverse events included the lowering of LVEF to 50% but no exacerbation of the coronary heart disease was ob-

served. During treatment, no TnI or NT-proBNP tests were made. After each chemotherapy, hematological toxicity was observed with severity not worse than grade 3 CTCAE, which involved a decreased granulocyte count (ANC 0.17 G/l) with accompanying febrile neutropenia and symptomatic anemia which required a transfusion of packed red cells – HGB min. 4.5 mmol/l. These complications tended to recur but were quickly resolved after proper measures were taken. Considering the advanced age of our patient and her cardiological diseases, the outcome of R-COMP therapy should be considered satisfactory and the adverse events – acceptable.

OFF-LABEL USE OF MEDICATION

Off-label use of drugs is a controversial issue due to ethical and legal considerations. There is no single act of common law in Poland which expressly regulates off-label use of medication.

The Medical Profession Act [14] stipulates that a doctor must practice their profession in accordance with the current medical knowledge, using prophylactic methods and measures available to them, and must recognize and treat diseases in compliance with professional ethics and standard of due care. Thus, a doctor must employ all measures which help to attain the intended goal, eliminating or reducing the risk to health [15]. A doctor must initiate therapy primarily using already registered medications and only when these prove inefficacious in curing a disease in a particular patient, the doctor may resort to other medication provided that it is used in accordance with the current medical knowledge. It should be noted that the doctor's obligation to practice medicine in accordance with the requirements of current medical knowledge is consistent with the patient's right to be treated in accordance with such requirements. Article 6 of the Act on Patient's Rights and Ombudsman for Patient's Rights states that patients have the right to receive medical care which conforms to the standards of the current medical knowledge. Oskar Luty believes that if no law explicitly forbids off-label use of drugs, it should be taken to mean that such use is legal as no such ban has been imposed [16]. If the law did forbid any off-label use of drugs, it would be impossible to receive a reimbursement of a drug used off-label on individual prescription from a doctor. As a guiding principle, a doctor should prescribe medications in accordance with the summary of the product characteristics (SPC) to ensure patients receive a safe and efficacious treatment [17]. The Pharmaceutical Law lays down the mandatory components of an application for a marketing authorization of a medicinal product. According to the law, the application should include the summary of prod-

uct characteristics (Article 10.2.11 of the Pharmaceutical Law). The mandatory elements of the SPC include, *inter alia*, product name, qualitative and quantitative composition, pharmaceutical form, dosage and form of administration for adults and children, if a given product is authorized to be used in pediatric patients (Article 11 of the Pharmaceutical Law). The provisions of common law do not provide a clear answer on the status of the SPC. The summary is not a legal standard with a general application but merely an instruction for medical personnel to follow when prescribing/administering a given drug. Doctors sent a petition to the Minister of Health postulating that patients should be treated in accordance with EBM rather than with the summary of product characteristics. On January 31st 2012, the Minister published an announcement [18] responding that the summary is a document that contains all the essential data about a drug obtained in clinical trials and is regularly updated on the basis of data obtained after the product is introduced to the market. It should be noted that the indications prescribed by the SPC are of fundamental importance and all alternative uses should be viewed as exceptional and may take place only in an emergency which cannot be remedied by any measures other than administering a specific drug [19]. In an extreme state of emergency, off-label use may be allowed with a proviso that it can be associated with a risk of legal liability for the entity providing medical care [20]. Deontological ethical standards for doctors also confirm the view that the doctor's decision is autonomous in relation to the patient. Article 6 of the code of ethics for the medical profession states that a doctor is free to choose the management method which they believe to be most efficacious and such decision lies with a specific doctor in relation to a specific patient [21]. This provision enables a doctor to freely choose the treatment method which is entirely up to the doctor's decision rather than the patient's decision. A doctor initiating a treatment of a patient has the duty to consider the risks involved in the treatment, and to only take such measures which maximize the benefits and minimize the harm to the patient [22]. In this context, one cannot forget about Article 31.1 of the Act on the Medical Profession which states that a doctor shall provide the patient or the patient's legal representative with comprehensible information about the patient's health status, diagnosis, recommended and available diagnostic and therapeutic methods, foreseeable effects of using or omitting to use the same, the treatment outcome and prognosis. Article 45 of the Act on the Medical Profession states that a doctor may prescribe drugs,

foods for particular nutritional uses registered in Poland under separate regulations, as well as medicinal products, devices for medicinal products, medicinal products for *in-vitro* diagnostic tests, devices for medicinal products for diagnostic tests, and active medicinal products for implantation within the meaning of the Act on Medicinal Products of May 20th 2010 [23].

Article 35a.4 of the Pharmaceutical Law (hereinafter: PL) states that the registration holder, manufacturer, authorized wholesaler or retailer, doctor or other individuals authorized to prescribe and dispense medicinal products under separate provisions are not subject to civil or disciplinary liability for the effects of using a medicinal product differently than in accordance with the indication prescribed by the registration or for effects of using a medicinal product which has not been registered provided that such use takes place under a temporary authorization issued by the Minister of Health pursuant to Article 4.8 of PL. This provision enables the Minister of Health to issue temporary authorizations for medicinal products which have not been registered in the event of a natural disaster or another threat to human or animal life and health. When deliberating on the possibility of using drugs off label, one must note the provisions of Article 27.1 of the Criminal Code. In accordance with the Code, no offence is committed by anyone who acts for the purpose of conducting a cognitive, medical, technical or economic experiment if the experiment is expected to bring significant cognitive, medical or economic benefits, and the expectation that such a benefit will be achieved, and the experiment's purpose and method are legitimate in light of the current scientific knowledge. Par. 3 states that the rules and conditions for admissibility are defined in the Act on the Medical Profession. In the opinion of Jan Kanturski, a doctor may prescribe a drug off-label also outside of the scope of a clinical trial and medical experiment provided that that doctor does not intend to commit a tort or expand the horizons of medical knowledge, and the medical methods used so far are insufficient [24].

In summary, the common law does not expressly forbid using drugs off-label. Furthermore, amended regulations make it possible to provide urgent medical care to patients, if justified by the circumstances, using medication which has so far not been paid for with public resources when used in a given indication. In certain clinical situations, off-label use is the only option available to the patient.

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