BHS guidelines on supportive care in lymphoma: Part 2

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SUMMARY

Besides disease-directed therapy, patients with lymphoma are in need of a wide range of supportive measures. In the second part of this guideline, the prevention and treatment of tumour lysis syndrome, cardiac support and physiotherapy are discussed.

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INTRODUCTION

In Belgium, lymphomas are the eighth most common malignancy and the most common haematological malignancy. They accounted for 3,8% of all new cancer diagnoses in 2020 and they are respectively the fifth and seventh most common cancer diagnosis in males and females based on incidence numbers.[1]

Treatment for lymphoma patients has undergone an increased complexity with several new agents available as therapy. These novel therapies increase the need for supportive care in this patient group. In this article, we reviewed the current available literature on supportive care for lymphoma patients.

TUMOUR LYSIS SYNDROME

Tumour lysis syndrome (TLS) is a haematological emergency. TLS is correlated with an increased overall mortality but is easily preventable.[2]

The pathogenesis is based on the fast lysis of malignant cells resulting in the release of intracellular content: potassium, phosphate, nucleic acids, proteins and their metabolites. These metabolites can overwhelm the body's normal homeostatic mechanisms and cause hyperuricemia (metabolisation product of nucleic acids), hyperkalaemia, hyperphosphatemia and hypocalcaemia. Deposition of uric acid and/or calcium phosphate crystals in the renal tubules can result in acute kidney injury. The rapid increase in potassium can lead to cardiac arrhythmias. Hypocalcaemia, a result of the binding of calcium to the high amount of available phosphorus, can result in tetany, arrhythmias and in severe cases in seizures. Although TLS can occur spontaneously, it is usually associated with the initiation of cytotoxic therapy.[3]

According to the Cairo-Bishop definition, TLS can be classified either as a laboratory diagnosis or as a clinical diagnosis.[4]

A laboratory TLS is defined as two or more of the following metabolic abnormalities: hyperuricemia, hyperkalaemia, hyperphosphatemia or hypocalcaemia. They need to be present within seven days after the initiation of chemotherapy. To include patients who present with signs of TLS before the initiation of chemotherapy the definition was

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TABLE 1. Cairo-Bishop definition of laboratory tumour lysis syndrome in adults.

Test	Value	Change from baseline
Uric acid	≥ 8 mg/dL (≥476 mmol/L)	25% increase
Potassium	≥ 6.0 mmol/L (≥6mEq/L)	25% increase
Phosphorus	≥1.45 mmol/L (≥4.5mg/dL)	25% increase
Calcium	≥ 1.75 mmol/L (≥7mg/L)	25% decrease
Laboratory TLS classified as abnormality of two or more laboratory changes as defined above.		

adjusted by Cairo and Bisschop. Following this adjustment, diagnosis of laboratory TLS could also be made if two or more abnormal values are present within three days before the initiation of chemotherapy (*Table 1*).

Clinical TLS is defined as laboratory TLS with one or more of the following clinical abnormalities: elevated creatinine levels (at least 50% above baseline level), cardiac arrhythmia/sudden death or seizures (all not attributable to a therapeutic agent).

When the diagnosis of a Clinical TLS is made it can be further categorised by the Cairo-Bishop grading classification from grade I (least severe) to grade V (leading to death). This grading system is based on the degree of elevation of the serum creatinine and the presence of clinical symptoms such as cardiac arrhythmias and/or seizures (*Table 2*).[2]

The pathogenesis of TLS allows a swift and very efficient prevention. This is mainly done by two actions:

The first is intravenous hydration, thus creating an optimal environment for the excretion of uric acid and phosphorus. Most guidelines advise a fluid input of 3L/m²/day or aim for a urinary output of at least 100 ml/h.[2]

The second is the reduction of uric acid serum levels through metabolisation. This can be done by several therapies:

ALLOPURINOL

The best known of these therapies is allopurinol, a xanthine oxidase inhibitor. It is seen as a backbone in the prevention of TLS in patients with haematological malignancies since the 1960's. It lowers serum uric acid by inhibiting the oxidation of xanthine and hypoxanthine to uric acid, thereby reducing the risk of uric acid crystallisation and consequently reducing the risk of renal failure. Median time of normalisation of uric acid levels is 24 hours when using allopurinol. Recommended dosing starts from 300 mg once daily up to 800 mg a day (divided into three doses a day). It should be started 1-2 days before the initiation of chemotherapy and continued until seven days after the end of the chemotherapy.[2]

FEBUXOSTAT

Febuxostat is another xanthine oxidase inhibitor that can be used in the prevention of TLS. Its working mechanism is similar to that of allopurinol but it has some theoretical advantages over allopurinol but has failed to demonstrate superiority in preventing TLS when compared to allopurinol.[2,5] In Belgium its use is obsolete in clinical practice.

RASBURICASE

Rasburicase is a recombinant urate oxidase. It catalyses the enzymatic oxidation of uric acid into allantoin, a metabolite that is ten times more soluble than uric acid. It has been shown to decrease uric acid levels significantly within four hours after administration and its potency for the rapid and drastic reduction of serum uric acid has been shown in multiple trials. When compared to allopurinol on clinical relevant endpoints such as renal failure and the need for dialysis, it has not shown any significant benefits in randomised trials. Despite this, rasburicase is the first choice in patients at high risk for TLS. Rasburicase is preferred because its enzymatic mechanism of action acutely decreases the already present levels of uric acid. In contrast, allopurinol only decreases the formation of uric acid but does not alter the serum levels of already circulating uric acid.[2]

Due to the significant higher cost of rasburicase compared to allopurinol; we suggest the use of rasburicase only in patients at high risk of TLS. Rasburicase should not be used in patients with a known 6-glucosis phosphate deficiency (6-GPD) because it can induce severe haemolysis. In patients

TABLE 2. Severity grading criteria for clinical TLS by Cairo and Bishop, 2014.

	Grade I	Grade II	Grade III	Grade IV	Grade V
Creatinine	1.5 x ULN*	>1.5-3 x ULN	>3-6 x ULN	>6 x ULN	Death
Cardiac arrhythmia	No intervention	Non-urgent medical intervention	Symptomatic, incompletely controlled with medical intervention or controlled with device	Life threatening	Death
Seizure	None	One brief generalised seizure or infrequent focal seizures not interfering with activity of daily life, well-controlled with medication	Altered consciousness during seizures, breakthrough seizures despite medical intervention	Seizure of any kind which is prolonged or difficult to control	Death

*ULN: Upper limit of normal.

at need for rasburicase with an African-American, Mediterranean or southeast-Asian descent, testing for 6-GPD should be done beforehand.[2,6]

The recommended dose of rasburicase is 0.2 mg/kg per day for up to five days.

OTHER SUPPORTIVE ACTIONS

Another action that could be used is the alkalisation of the urine by administration of sodium bicarbonate. This can lead to a decreased formation of uric acid crystals in the urine and thus to a better clearing of uric acid in the serum. Despite this effect, its use is currently made obsolete because of a paradoxical side effect when used in association with allopurinol. The alkalisation of the urinary pH causes a decrease in the solubility of xanthine, leading to an increase in the formation of xanthine crystals that can cause renal damage. Alkalisation also tends to increase the formation of calcium phosphate crystals.[2,6]

In the management of patients with established tumour lysis syndrome, continuous cardiac monitoring is advised. If possible, this should be done at an Intensive Care Unit (ICU). Measurement of electrolytes, kidney function and uric acid levels every four to six hours is advised. Treatment with rasburicase should be initiated in combination with sufficient IV fluid administration if not yet started. Correction of electrolyte abnormalities should be done. There should be attention for the treatment of hyperkalemia because of its potential life threatening risks. In case of renal failure, advice of an expert in renal medicine should be asked and if needed, renal replacement therapy should be considered.

A risk model for predicting which patients are at highest risk for TLS, and thus whom may require increased surveillance and treatment for TLS, has been made in 2010 by an international panel.[5]

Patients are divided into three risk categories; low-risk (<1% chance on TLS), intermediate risk (1-5% change on TLS) and high risk (>5% change on TLS).

Lymphoma patients are divided in these risk groups according to pathology. Patients with Burkitt lymphoma are always considered high risk. Patients with diffuse large B-cell lymphoma, peripheral T-cell lymphoma, transformed lymphoma and blastoid mantle cell lymphoma are generally considered as intermediate risk. They become high risk when there is bulky disease or when serum LDH levels are equal or higher than twice the upper normal value. Small lymphocytic, follicular lymphoma, marginal zone lymphoma, non-blastoid mantle cell lymphoma and cutaneous T-cell lymphoma are all considered low risk for TLS.[2,4]

CARDIAC SUPPORT

Many cardiotoxic effects are attributed to the use of chemotherapy. These include cardiomyopathy, QT prolongation, myocardial infarction, pulmonary hypertension and increased incidence of thrombosis.[7,8] The most important causes of cardiotoxicity due to lymphoma treatment are the use of anthracycline-based chemotherapy and the use of radiotherapy on the thoracic region.

TABLE 3. Comparison of incidence of LV dysfunction induced by clinically used doxorubicin-derivatives.

Anthracycline	Incidence of LVSG/HF
Doxorubicin	7-26% at 550 mg/m²
Epirubicin	0.9-11.4% at 900 mg/m²
Idarubicin	5-18% at >900 mg/m²
Liposomal doxorubicin (Myocet™)	2% at 900 mg/m²

ANTHRACYCLINES

The most common cardiotoxic side effects of anthracyclines are left ventricular dysfunction and heart failure. Less common events are cardiac arrhythmias and myocarditis.[8-10]

The cardiotoxicity profile of anthracyclines is thought to be mediated either through the inhibition of topoisomerase 2-beta in cardiomyocytes, finally leading to increased production of reactive oxygen species (ROS) and thus cardiac cell death, or via direct generation of ROS leading to DNA damage, protein carobonylation and lipid peroxidation.[7,9,11]

The older generations of anthracyclines like daunorubicin and doxorubicin have the highest cardiotoxic risk profile. The newer generations have a lower cardiotoxic risk profile.[8] These include idarubicin, epirubicin and mitoxantron. Liposomal formulations of doxorubicin are considered less cardiotoxic than non-liposomal formulations. Unfortunately, these formulations are not approved in the treatment of lymphoma patients.[9]

Cardiotoxicity of anthracyclines is dose dependent and cumulative.[7,12]

The cumulative incidence of cardiac events after treatment with anthracyclines peaks around 1 year after treatment.[8] It is generally agreed that a cumulative dose higher than 500 -550 mg/m² of doxorubicin shows a marked increase in heart failure and is therefore seen as a threshold not to be crossed.[7,8] The incidence of heart failure is respectively 4.7%, 26% and 48% for patients receiving doxorubicin in doses of 400 mg/m², 550 mg/m² and 700 mg/m².[10] The most commonly accepted threshold levels for different anthracyclines are shown in *Table 3*.[13]

Risk factors on development of anthracycline induced heart failure are age < 5 or > 65 years, cumulative dose of anthracyclines, previous anthracycline use, prior radiotherapy to chest or mediastinum, female sex, classical cardiovascular risk factors (family history of premature cardiovascular disease, arterial hypertension, diabetes mellitus, smoking, obesity, sedentary habit and hypercholesterolemia), high alcohol intake and pre-existing cardiac disease.[9,14]

Following the European Society of Cardiology (ESC) guidelines, the best applicable definition of chemotherapy-related cardiotoxicity is a decrease of the left ventricular ejection fraction (LVEF) of at least 10% from the baseline value to a value of 53% or less on repeated echocardiographic imaging in chemotherapy-exposed individuals.[15]

Some additional methods for detection of cardiotoxicity beyond LVEF include serum biomarker levels, myocardial strain (a measure of deformation) using echocardiography and detection of myocardial fibrosis using cardiac magnetic resonance.

Cardiac MRI is currently investigated as means for follow-up of cardiac function instead of echocardiography, but it is currently not yet recommended as routine follow-up and is less available than echocardiography and might not be cost-effective.[8]

The use of biomarkers like troponin and Brain type Natriuretic Peptide (BNP) is being investigated as ways for the early detection of cardiotoxicity. Elevated troponin levels after treatment and sustained levels for at least one month have been shown to be a predictor of anthracycline-induced cardiotoxicity. Of interest, a rise in troponin levels has been observed after only the first dose of anthracyclines.[15,16]

Some studies have found a correlation between elevated Brain type Natriuretic Peptide (BNP) and cardiotoxicity of anthracyclines. Unlike troponins, this correlation has not yet been proven in large prospective studies and therefore BNP cannot be advised as a valid biomarker for risk of cardiotoxictity.[8,17]

The main strategy in controlling anthracycline related cardiotoxicity remains the early detection of left ventricular dysfunction and initiating standard treatment for

TABLE 4. Recommended follow up of LVEF.

Timing of LVEF measurement	Patient group
Before initiation of chemotherapy	All patients
≥ 240 mg/m² doxorubicin (or equivalent)	High risk patients Higher-dose anthracycline containing chemotherapy
End of treatment	All patients
6 months after end of treatment	Optional in all patients
24 months after end of treatment	
36 months after end of treatment	

heart failure (angiotensin converting enzyme inhibitors, beta-blockers, etc.). For screening, the European Society of Cardiology position paper in 2016 has put forward following advice:[15]

- The same imaging modality/biomarker assay should be used for continuous screening throughout treatment.
- Modalities with the best reproducibility are advised.
- Imaging modalities that provide additional relevant clinical information are advised (e.g. right ventricular function, pulmonary pressure, valvular function, pericardial information).
- If available, high quality radiation-free imaging is preferred.

It is recommended to measure the baseline LVEF before initiation of treatment in all patients undergoing anthracycline-based chemotherapy.

In patients undergoing a higher-dose anthracycline containing chemotherapy and in high-risk patients, assessment of cardiac function should be considered after a cumulative total dose of 240 mg/m² doxorubicin (or equivalent).

Follow-up cardiac imaging is recommended in all patients after completion of chemotherapy.[8,9]

Some guidelines recommend follow-up of imaging at 6, 24 and 36 months after completion of chemotherapy.[18]

As imaging modality for measuring cardiac function, echocardiography is preferred over the use of radioisotopes based methods such as multiple gated acquisition (MUGA) scan, which exposes the patient to radiation. In addition, echocardiography offers more information (e.g. diastolic function, valvular evaluation) than just the measurement of LVEF compared to MUGA. If available, 3D echocardiography should be preferred over 2D due to its higher reproducibility.

Table 4 summarises the current recommendations for cardiac follow up.

Preventive treatment with heart failure therapies (ACE-inhibitors, angiotensin II receptor blockers and beta-blockers) in all patients treated with anthracycline-based chemotherapy has very limited positive effects on prevention of LVEF decrease. Therefore, this is not advised in clinical practice.[9]

Some retrospective data suggest that the use of statins and their anti-inflammatory effects could have a protective effect on adriamycine-related cardiotoxicity. Studies investigating this effect have described positive effects in animal models but no prospective data exist on this matter. Therefore, the use of statins in prevention of adriamycine related cardiotoxicity is currently not recommended.[9]

Dexrazoxane is used to prevent anthracycline-induced cardiotoxicity, mainly in breast cancer patients. It is an analogue of the iron chelator ethylenediaminetetraacetic acid (EDTA) and its mechanism of action is not yet fully understood. Dexrazoxane is hypothesised to chelate intracellular iron, block iron-assisted oxidative radical production and inhibit the topoisomerase II-beta isoenzyme, which has been implicated in anthracycline induced cardiotoxicity.[9,12] In Europe, it is currently only approved for use in extravasation of anthracylines and not for prevention of anthracyline-related cardiotoxicity.[8,9]

In the case of documented heart failure caused by anthracyline-based treatment, the patient should be referred to a cardiologist, specialised in cardio-oncology. We also recommend referral when an asymptomatic decline of the LVEF is detected. Appropriate heart failure therapy should be commenced following the ESC heart failure guidelines. This concerns treatment with an ACE-inhibitor or angio-

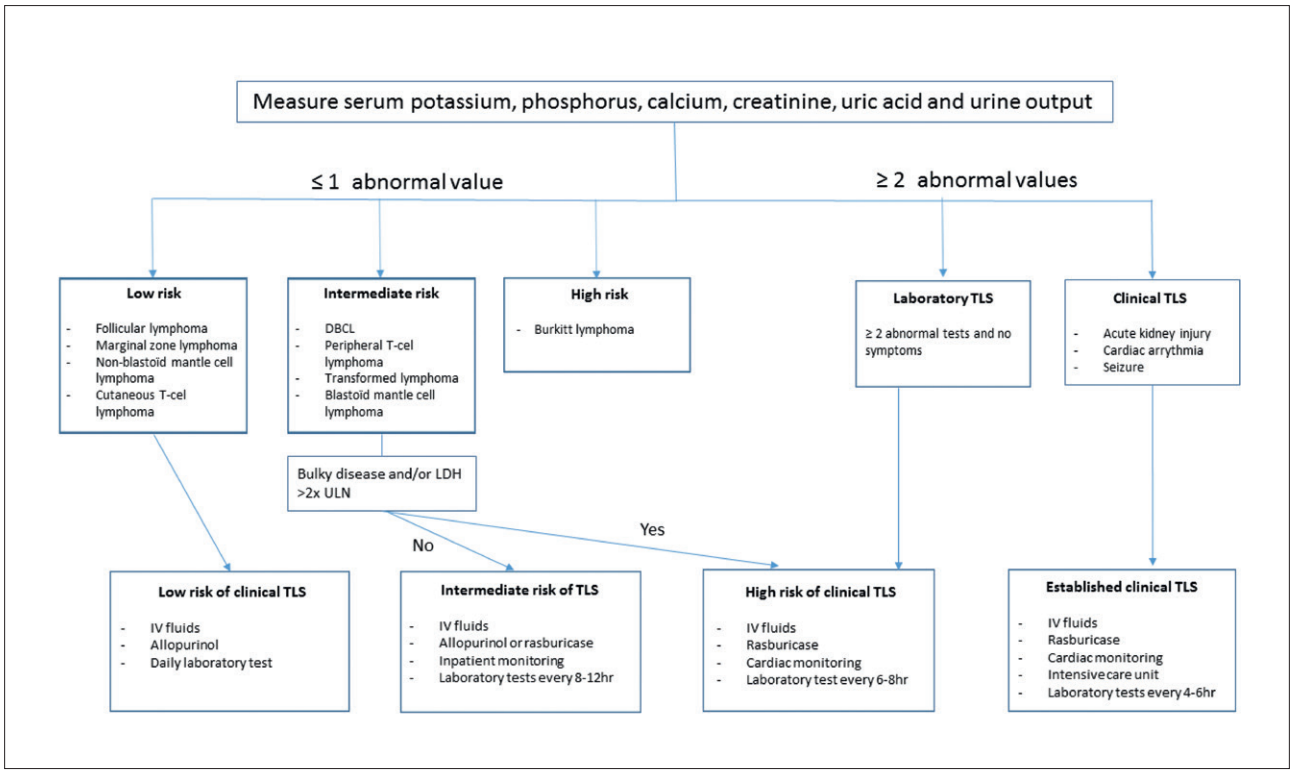

FIGURE 1. Tumour lysis syndrome (TLS) treatment stratification algorithm.

tensin receptor blocker, alone or in combination with a beta-blocker. The earlier this therapy is initiated, the higher the chance of recovery of the LVEF to normal levels.[9] Unfortunately, in clinical practice often a relatively low blood pressure limits uptitration to the target dose.

RADIOTHERAPY

As with anthracycline-induced cardiotoxicity, there is a clear dose dependent correlation between radiotherapy dose and its cardiotoxic effects.[17]

The most common cardiotoxic side effect from radiotherapy is valvular heart disease, coronary heart disease followed by heart failure and pericardial abnormalities.[13] Current developments such as intensity-modulated radiotherapy, volumetric modulated arc therapy and deep inspiration have made a significant decrease in radiotherapy dose possible and by doing so, facilitated a reduction in cardiotoxic effects. Newer techniques are in development to further reduce the cardiotoxic effects of radiotherapy, for example proton therapy.

Although there are no international guidelines, screening of patients with echocardiography, cardiac perfusion imaging, stress testing and/or coronary calcium scoring by computed tomography (CT) is considered if the coronary arteries received >35 Gy of irradiation exposure beginning five years after therapy or after age 30-35 years, whichever is last.[13]

PHYSIOTHERAPY

Patients with haematological malignancies have to endure long phases of therapy and immobility, which is known to diminish their physical performance level. They often have reduced functional performance due to the cancer itself or as a direct side effect of cancer treatment. The advice to rest and to avoid intensive exercises is still common practice, due to the severe anaemia and thrombocytopenia from which many patients suffer. The inability to perform activities of daily living restricts them, diminishes their quality of life and can influence medical therapy. In a study of *Knips et al.* eighteen randomised controlled trials were included comparing an aerobic physical exercise intervention, intended to improve the oxygen system, in addition to standard care with standard care only for adults suffering from haematological malignancies. They could not identify evidence for a difference in terms of mortality, but physical exercise added to standard care might improve fatigue and depression.[19]

Physical interventions must be used with caution with respect to bone disease, thrombocytopenia, anaemia, fever, infection, postoperative status and safety issues like risk of falling. An exact exercise program does not exist.

CONCLUSION

Supportive measures remain an important part of the

KEY MESSAGES FOR CLINICAL PRACTICE

1 **Quality of life during treatment can be significantly increased by adequate adherence to supportive care such as correct use of ant-emetics.**

2 **Outcome and reduction of complications during and after treatment can be significantly improved by supportive measurement such as use of G-CSF, cardiac follow-up, correct management of tumour lysis profylaxis, etc.**

treatment of patients with lymphomas. Not only can supportive treatment increase the quality of life of patients who undergo treatment but they can also have an important impact on outcome and reduction of complications following the treatment and the disease.

REFERENCES

1. World Health Organisation: International Agency for Research on Cancer (IARC). Belgium fact sheets [internet]. Lyon, France: IARC; 2020. Available form https://gco.iarc.fr/today/data/factsheets/populations/56-belgium-fact-sheets.pdf
2. Durani U, Hogan WJ. Emergencies in haematology: tumour lysis syndrome. Br J Haematol. 2020;188(4):494-500.
3. Howard SC, Jones DP, Pui C-H. The tumour lysis syndrome. N Engl J Med. 2011;364(19):1844-54.
4. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification: New Therapeutic Strategies and Classification of TLS. Br J Haematol. 2004;127(1):3-11.
5. McBride A, Westervelt P. Recognizing and managing the expanded risk of tumour lysis syndrome in hematologic and solid malignancies. J Hematol Oncol. 2012;5(1):75.
6. Spina M, Nagy Z, Ribera JM, et al. FLORENCE: a randomized, double-blind, phase III pivotal study of febuxostat versus allopurinol for the prevention of tumour lysis syndrome (TLS) in patients with hematologic malignancies at intermediate to high TLS risk. Ann Oncol. 2015;26(10):2155-61.
7. Moudgil R, Yeh ETH. Mechanisms of cardiotoxicity of cancer chemotherapeutic agents: Cardiomyopathy and beyond. Can J Cardiol. 2016;32(7):863-870.e5.
8. Chung W-B, Youn H-J. Pathophysiology and preventive strategies of anthracycline-induced cardiotoxicity. Korean J Intern Med. 2016;31(4):625-33.
9. Henriksen PA. Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention. Heart. 2018;104(12):971-7.
10. Marinello J, Delcuratolo M, Capranico G. Anthracyclines as Topoisomerase II poisons: From early studies to new perspectives. Int J Mol Sci. 2018;19(11):3480.
11. Sawyer DB. Anthracyclines and heart failure. N Engl J Med. 2013;368(12):1154-6.
12. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(36):2768-801.
13. Nebigil CG, Désaubry L. Updates in anthracycline-mediated cardiotoxicity. Front Pharmacol. 2018;9:1262.
14. Lipshultz SE, Rifai N, Sallan SE, et al. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. Circulation. 1997;96(8):2641-8.
15. Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of anthracyclines. Front Cardiovasc Med. 2020;7:26.
16. Koutsoukis A, Ntalianis A, Repasos E, et al. Cardio-oncology: A focus on cardiotoxicity. Eur Cardiol. 2018;13(1):64-9.
17. Zhang J, Cui X, Yan Y, et al. Research progress of cardioprotective agents for prevention of anthracycline cardiotoxicity. Am J Transl Res. 2016;8(7):2862-75.
18. Ratosa I, Ivanetic Pantar M. Cardiotoxicity of mediastinal radiotherapy. Rep Pract Oncol Radiother. 2019;24(6):629–43.
19. Knips L, Bergenthal N, Streckmann F, et al. Aerobic physical exercise for adult patients with haematological malignancies. Cochrane Database Syst Rev. 2019;1(1):CD009075.