Cardiotoxicity from anthracycline and cardioprotection in paediatric cancer patients

Pier P. Bassareo, Ines Monte, Claudia Romano, Martino Deidda, Alessandra Piras, Lucia Cugusi, Carmela Coppola, Francesca Galletta and Giuseppe Mercurio

Notwithstanding the steady progress in survival rates of children and adolescents suffering from cancer, the benefits associated with chemotherapy do not come without risks involving multiple organs and systems, including the cardiovascular apparatus. Anthracyclines—often administered in combination with radiation therapy and/or surgery—are the most used chemotherapeutic compounds in order to treat tumours and blood malignancies even in paediatric age. Being an important side-effect of anthracyclines, cardiotoxicity may limit their efficacy during the treatment and induce long-term sequelae, observed even many years after therapy completion. The purpose of this review was to perform an overview about all the possible strategies to prevent and/or limit the anthracyclines adverse side-effects for the cardiovascular system in childhood cancer survivors.

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Introduction
The steady progress in the pathophysiological knowledge and therapy has led to an increase in the survival rates of children and adolescents suffering from malignancies (in the United States about 270 000/year). Specifically, in the period 1975–2005 the US young survivors aged less than 15 years have increased from 58% (1975–1978) to 81% (1999–2005) (Table 1).

The cardiotoxicity (CTX) may be a serious side-effect of cancer therapy, both at the time of its administration and follow-up. Indeed, the adverse cardiovascular events are the leading cause of death, not because of cancer, in these young patients, being their risk seven times higher than their healthy peers. Anthracyclines are among the most antineoplastic drugs administered and efficient even in childhood. However, they can cause a number of serious cardiovascular side-effects in the short, medium and long periods of time. For example, about 20% of cancer survivors may develop a dilated cardiomyopathy, even at 15–20 years after the administration of these compounds. Moreover, radiation therapy, often administered in combination with chemotherapy, can increase the risk of pericardial disease, myocardial fibrosis, arrhythmias, valvular abnormalities and early coronary artery disease in these still so young patients. The search strategy of this study has been summarized in Table 2.

Few studies have investigated the prevalence worldwide of anthracycline-induced adverse cardiovascular events in adult and adolescent population, former paediatric cancer patients.

Although in Italy, this information is limited to small number of patients and cardiovascular outcomes produced by single centers, in the United States, these studies involved a very large number of subjects, with widely detailed information. The Childhood Cancer Survivor Study is the largest study on cardiovascular adverse events related to antihistamine therapy, at 5 years or more after the cancer diagnosis.

The childhood cancer survivors study
In a multicenter retrospective observational study involving 26 US institutions, 14 358 patients (53.7% males) were recruited. All study subjects were cancer survivors, diagnosed before the age of 21, with leukaemia, brain cancer, Hodgkin’s and non-H Hodgkin’s lymphoma, kidney cancer, neuroblastoma, soft tissue sarcoma or bone cancer. A questionnaire was given to all patients, or their parents, if under 18 years.

The outcomes of the research were the prevalence and rates of cardiovascular disease, such as congestive heart failure (with or without dilated cardiomyopathy), myocardial infarction, pericardial disease (pericarditis or pericardial constriction) and valvular abnormalities (leaffets thickening or cleft). The comparison group included 3899 siblings of cancer survivors. The observation period was 1970–1986. The majority of patients in the study
(42.3%) was aged between 20 and 29 years (mean 27 years). In detail, 70.7% of them had been treated with chemotherapy and radiotherapy, 18% with chemotherapy combined with surgery, 11% with radiotherapy and surgery, and 0.3% with radiotherapy alone.

The results of the Childhood Cancer Survivors Study (CCSS) showed that among the survivors, the prevalence of congestive heart failure is significantly higher than in controls (1.7 vs. 0.2%, \( P < 0.001 \)). Moreover, the prevalence of myocardial infarction, pericardial disease and valvular abnormalities were 0.7, 1.3 and 1.6% among the survivors, in comparison with 0.2, 0.3 and 0.5% in the control group (all \( P < 0.001 \)).

As it regards the different therapeutic options, treatment against leukaemia induced, above all, congestive heart failure and valvular abnormalities; treatment against brain cancer was responsible for myocardial infarction; Hodgkin's lymphoma, neuroblastoma and bone cancer, as they were placed in relation with all the cardiovascular adverse events, showed no significant differences from the control group. The non-Hodgkin's lymphoma and sarcoma were associated with all the possible cardiovascular side-effects, with the exclusion of myocardial infarction. Finally, the therapy of kidney cancer was related only with congestive heart failure and valvular dysfunction.

As regards each type of adverse cardiovascular events, heart failure was the most common manifestation of female patients under the age of 4 years treated in the period 1980–1986 with a dose of anthracyclines above 250 mg/m², still more if radiotherapy (dose >1500 cGy) was added. Myocardial infarction was more frequent in females than in males, especially if the radiation dose was higher than 1500 cGy. No relationship with the administered dose of anthracycline was found.

In contrast, patients with pericardial disease were, above all, males treated with anthracyclines (>250 mg/m²). This association was stronger if these individuals had been treated with cyclophosphamide, as well as radiation more than 1500 cGy. Valvular abnormalities were common among women under the age of 9 years treated with anthracycline dose of more than 250 mg/m² and radiation more than 1500 cGy in the period 1980–1986. The aforementioned anomalies were not more serious if the radiation dose was higher. The most common long-term side-effect of anthracyclines was congestive heart failure (8% of the patients, as late as 30 years after therapy). Strengths and weaknesses of the CCSS, which is the most extensive research in the world on this subject, have been summarized in Table 3.

In conclusion, CCSS has confirmed that cardiovascular events are the non-neoplastic leading cause of death among survivors of childhood and adolescence cancer. This risk becomes apparent for exposure to lower doses of anthracyclines and radiotherapy than had been previously recognized.\(^a\)

### Anthracycline-induced cardiotoxicity: the Italian expertise

In Italy, studies like the CCSS are lacking. Limited data come from small case series, with limited sampling and cardiovascular outcomes. However, they essentially confirm the anthracycline-induced CTX.

For example, Cipriani et al. (San Donato Milanese) showed a systolic and diastolic dysfunction in a small sample (\( n = 18 \)) of young patients (mean age 11.5 years) treated with anthracyclines. The effect became evident at a dose exceeding 250 mg/m² (average dose 317 mg/m²). The median time of occurrence was 5.8 since the beginning of therapy, while 2.8 years from the end of administration.\(^b\)

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**Table 1** Survival rates (%) for American children aged under 15 years and suffering from cancer\(^a\)

<table>
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<tr>
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<tbody>
<tr>
<td>Acute lymphocytic leukaemia</td>
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<tr>
<td>Acute myeloid leukaemia</td>
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<td>60</td>
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<tr>
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<td>72</td>
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<tr>
<td>Brain cancer</td>
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<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>44</td>
<td>86</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>61</td>
<td>81</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>73</td>
<td>91</td>
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**Table 2** Search strategy

A PubMed/MEDLINE search has been conducted using the MeSH terms: anthracycline, doxorubicin, epirubicin, daunorubicin, cardiotoxicity, heart failure, coronary artery disease, pericardial (pericardium) disease, valvular (valve) disease, imaging, echocardiography, cardiac magnetic resonance, stress test, cardiac biomarkers, troponin(s), pro-BNP, BNP, ANP, high sensitivity C-reactive protein, liposomal anthracyclines, antioxidant agents, sildenafil, phosphodiesterases inhibitors, adiponectin, erythropoietin, and their combinations. Articles identified in this manner were retrieved and the reference lists searched for additional relevant articles. The search was limited to English-language publications, but no other restrictions were applied. The PubMed/MEDLINE database was searched from its inception to August 2015. The papers of key importance are reported in this review.

ANP, Atrial natriuretic peptide; NT-proBNP, N-Terminal Brain Natriuretic Peptide Precursor.
These results show a cardiac damage early and not easily detectable.

Another commendable Italian study was from Gaslini Institute (Genoa), in which a subclinical cardiac dysfunction was demonstrated with an anthracycline dose higher than 240 mg/m² (therapeutic range 100–490 mg/m²). It manifested itself in a reduced peak oxygen consumption during exercise.¹¹

**Anthracyclines-induced cardiotoxicity in paediatric population**

The late cardiotoxic side-effects are those appearing at least 1 year after chemotherapy has been completed, and generally have a chronic course.¹²,¹³

Lipshultz found that, after 6 years of anthracyclines chemotherapy, about 65% of children have functional and/or structural left ventricle (LV) abnormalities.¹²,¹⁴ Late anthracycline CTX may be because of the fact that cardiomyocytes are not able to provide the energy requirements coming from children body growth, or stressful situations (e.g. pregnancy or viral infections).¹⁵,¹⁶ The severity of CTX may depend on the age of the patient.¹⁵ In fact, chemotherapeutics administered before completion of growth may sharply reduce the number of cardiomyocytes available for a positive cardiac remodelling.

**Cardiotoxicity prevention strategies in paediatric cancer patients**

The prevention of anthracycline-induced CTX is crucial in children and adolescents, who potentially have a life expectancy of several decades. To accomplish this, it is necessary to identify patients at high risk and adopting any possible preventive strategy.

**The role of imaging in the monitoring cardiac function**

At present, specific evidence-based Guidelines on evidence of anthracyclines-induced CTX in children and adolescents are lacking.

Although, most of the National Societies of Cardiology suggest to use echocardiography in order to monitor cardiac function in these patients. Specifically, the American Heart Association recommendation (evidence level Ia) is to perform an echocardiographic monitoring in children and adolescents treated with anthracyclines before, during, and after therapy.¹⁷ At the same way, United States Children’s Oncology Group recommendations suggest to perform a series of echocardiographic examinations, whose frequency depends on the patient’s age, previous traditional cardiovascular risk factors, anthracyclines cumulative dose and possible combination with radiotherapy.¹⁸ However, in none of the suggested protocols were the achieved practical results valorized. In fact, in clinical practice, every change detected in echocardiography produced change or discontinuation of antineoplastic treatment, but in none of the published studies was it evaluated whether these modes of monitoring would improve the quality and life expectancy of the young patients.

Therefore, although general agreement on the monitoring of these patients by echocardiography exists, specific scientific evidence on this subject are not available.¹⁵,¹⁹–²¹ The late anthracycline-induced CTX (5–10 years after therapy) suggests to monitor patients by echocardiography at least at the end of cancer treatment. However, as anticipated, no studies have focused on the desirability of personalized controls (tailored monitoring).²²–²⁴ Regarding echocardiography, since the M-mode measurements (e.g. fractional shortening) are frequency and volume overload dependent, the two-dimensional analysis of segmental and global LV contractility (ejection fraction) seems to reflect better the systolic function of the heart.²³,²² Again, it is important to note that data on a possible relationship between these echocardiographic measures and cardiovascular morbidity and mortality are not present in the literature.

Recent reports suggest that tissue Doppler imaging (TDI) and, especially, strain and strain rate modalities prove to be the most promising in the first months to describe the anthracycline-induced decline of LV systolic function.²⁵ The late anthracyline-related cardiomyopathy has been also studied by means of nuclear ventriculography, which appeared superior to traditional echocardiography in the study of systolic function in paediatric cancer patients.¹⁵ Although echocardiography is less invasive and does not require anaesthesia, ventriculography, which measures the change in the LV walls radioactivity between systole and diastole, can more accurately calculate the ejection fraction in these young patients. Moreover, it seems more effective in detecting early diastolic dysfunction.¹⁵ Some studies suggest to perform every 5 years a nuclear ventriculography in children and adolescents who survived cancer; but in clinical practice a frequent echocardiographic monitoring is greatly preferred.²⁶,²⁷ Cardiac magnetic resonance is a promising imaging technique in adult patients, but its effectiveness in children is unknown.²⁸

**The role of markers in monitoring cardiac function**

The cardiotoxic cardiac injury may remain latent for many months or years after treatment. Therefore, the possibility of identifying in advance the relationship between the administered dose of medication and the corresponding level of cardiac damage plays a crucial role. Furthermore, oncologists often adapt chemotherapy protocols used in adult patients to children, simply reducing the dosage in function of their weight. This strategy does not protect from side-effects: in fact, children are more vulnerable than adults are to anthracyclines.²⁹ Many
Cardiac troponins are proteins involved in the contractile system of cardiac cells. Furthermore, troponins are markers of myocardial necrosis, with blood concentrations exactly representative, in patients with a normal renal function, of degree of cardiac injury.\textsuperscript{15,17,31–37} The results in this area are, so far, limited and conflicting.\textsuperscript{35,37} Lipshultz et al.\textsuperscript{30} showed that, in paediatric patients treated with doxorubicin, small increases in troponin I levels are related with the thickening of cardiac walls and LV dilation, in a better way than other enzymes such as total Creatine-phosphokinase, Creatine-phosphokinase MB isoform and myoglobin. On the other hand, in young patients suffering from a specific cancer (acute lymphoblastic leukaemia), troponin T levels in the blood are not related with the earlier-stated echocardiographic alterations.\textsuperscript{35} The dosage of troponin T subtype in a group of patients aged 9–18 years, revealed no relationship with the doses of anthracyclines.\textsuperscript{38}

Brain natriuretic peptide (BNP) is released from stretched LV myocardial cells and is related to volume overload (e.g. in case of congestive heart failure).\textsuperscript{39,40} Even a BNP fragment, named N-Terminal Brain Natriuretic Peptide Precursor (NT-proBNP), is able to predict adverse cardiovascular events and cardiac death in patients with chronic heart failure, acute coronary syndrome and arterial disease.\textsuperscript{41,42} The increase in the plasma concentration of NT-proBNP within the first 90 days of chemotherapy is predictive of a delayed (up to 4 years) cardiac remodelling in children with acute lymphoblastic leukaemia. Therefore, NT-proBNP is able to predict an irreversible cardiac damage before its instrumental and clinical onset.\textsuperscript{30} However, other results seem to come to opposing evidence. In patients treated with doxorubicin 240 mg/m\textsuperscript{2} for acute lymphoblastic leukaemia, levels of BNP and NT-proBNP were normal, whereas for a dose of the drug of 120 mg/m\textsuperscript{2}, the TDI systolic and diastolic functions were already abnormal.\textsuperscript{43} In a retrospective study on 50 paediatric patients with acute leukaemia, TDI was able to detect a diastolic dysfunction in 60\% of cases, whereas NT-proBNP was altered in only 20\%, and troponin T in none.\textsuperscript{44} Atrial natriuretic peptide was slightly modified in a small sample of patients treated with doxorubicin and left ventricular dysfunction, but these results must be confirmed by more extensive observations.\textsuperscript{45}

Other promising research in paediatric cancer subjects concerns the high-sensitivity C-reactive protein, a marker of generalized inflammation.\textsuperscript{17,30} Again, larger and extended studies are needed to determine the actual ability of this marker in detecting myocardial damage induced by chemotherapy in the short, medium and long-term follow-up.\textsuperscript{17,32,46–48}

The role of stress test in monitoring cardiac function

Stress test is useful to detect asymptomatic cardiac dysfunction in adult cancer patients after anthracycline therapy coupled with mediastinal radiotherapy. Conversely, it is not known whether these results can be applied to children and adolescents, whose apparently normal baseline cardiac function may become abnormal in case of increased cardiac work.\textsuperscript{49–51}

Unanimously, the oxygen consumption of patients is reduced compared with healthy peers.\textsuperscript{52} In adult cancer patients with heart failure, two questionnaires on quality of life, the Minnesota Living with Heart Failure Questionnaire and the RAND-36ph, were administered. Physical capacity, tested with the 6-min walk test, appeared correlated with test scores of Minnesota and RAND-36ph and with NYHA class.\textsuperscript{53} In this area, it is not known whether these results can be applied in childhood.

In long-term Hodgkin’s lymphoma survivors, stress test coupled with oxygen consumption is closely related with prognosis. Actually, the oxygen consumption of these patients is reduced when compared with that of their healthy peers.\textsuperscript{52} In adult cancer patients with heart failure, two questionnaires on quality of life, the Minnesota Living with Heart Failure Questionnaire and the RAND-36ph were administered. The physical ability was tested with the 6-min walk test, which correlated with test scores of Minnesota and RAND-36ph, as well as with NYHA class.\textsuperscript{53} Also in this context, it is not known whether these results can be applied in childhood.

Strategies of cardioprotection

Reducing anthracyclines cumulative dose

The best hypothetical cardioprotective strategy would be to avoid anthracyclines administration, if an equivalent therapeutic response could be guaranteed.\textsuperscript{54} However, because of the lack of conclusive randomized studies, at the moment the actual chemotherapeutic protocols cannot be rejected. It is well known that higher doses of anthracyclines produce proportional worse cardiovascular side-effects. Nevertheless, lower doses are not free of cardiotoxic consequences.\textsuperscript{55} Given that the CTX can occur very late, it is really hard to determine the dose of anthracyclines at the same time efficient and with no side-effects. At this moment, in the majority of chemotherapeutic protocols, the maximum administrable dose of doxorubicin is of 450–550 mg/m\textsuperscript{2} and of epirubicin 900 mg/m\textsuperscript{2}.\textsuperscript{10,56–58} The study CCSS, however, showed that the CTX may also appear for doxorubicin 250 mg/m\textsuperscript{2}.\textsuperscript{2,30} In a recent Cochrane Library review, it was shown that only in paediatric patients with acute lymphoblastic leukaemia anthracyclines can be avoided without detriment regard to the chemotherapeutic effectiveness; but this strategy is not eligible for other types of cancer.\textsuperscript{59}
Modify anthracyclines modality of administration

The anthracycline continuous infusion, avoiding a sharp rise in the drug maximum plasma concentration, is able to reduce the cardiovascular side-effects in adults but not in children with acute lymphoblastic leukaemia.60–64

Administration of anthracyclines analogues and antracenediones

Some anthracycline analogues were synthesized, theoretically with the same efficacy, but with fewer cardiotoxic effects (epirubicin idarubicin and mitoxantrone).65–70 However, the results in the clinical context appear inconclusive.71–74

Liposomal anthracyclines

The liposomal anthracyclines diffuse especially in hypervascular areas, as are cancer cells, and therefore, prove to be more selective and efficient and less cardiotoxic than traditional formulations, in adult patients.75–78 Another advantage is their low release, which results in reduced circulating peak of these molecules and a more contained CTX.79 To date, three liposomal anthracyclines were tested: pegylated liposomal doxorubicin, liposomal doxorubicin and liposomal daunorubicin. This last seems even less cardiotoxic than the other.80–82

In a randomized trial in adults with metastatic breast cancer, pegylated liposomal doxorubicin was compared with the traditional formulation. Survival rates were similar between the two groups, but in patients treated with liposomal doxorubicin the CTX was less than in the other.82 Similar studies in children are limited and less conclusive.82 In an extensive review of liposomal anthracyclines administered in the paediatric population, only 15 publications were considered eligible.83 The conclusions of the review were that, to the best of our knowledge, there is not enough scientific evidence to prefer liposomal anthracyclines during childhood. On the contrary, in this age, a large number of side-effects have been reported (allergic reactions, mucositis, infections and liver toxicity).

Dexrazosane

Dexrazosane is an inhibitor of DNA topoisomerase-II, with an iron-chelating action capable of removing free iron, as well as that linked to doxorubicin, thus avoiding the formation of free radicals and attenuating the CTX.82,84 As the enzyme DNA topoisomerase-II is absent in cardiac cells, some doubts have been raised about the concrete protective action of dexrazosane.82 Despite these concerns, dexrazosane has proven to be a cardioprotective agent both in adults and in children.86,85–90 Data of Dana–Farber Cancer Institute Childhood Acute Lymphoblastic Leukemia (1995–2001) showed that dexrazosane reduces the anthracycline-induced cardiac damage in a mean follow-up of 2.7 years.35,36

Such long-term cardioprotective effect has been confirmed until a mean observation time of 8.7 years. The echocardiographic parameters were better in patients treated with the combination of doxorubicin and dexrazosane, compared with those treated with doxorubicin alone.90 Other concerns were raised about a possible paradoxical effect of dexrazosane in protecting not only the cardiomyocytes, but also cancer cells.91 A meta-analysis dissipated these doubts. The conclusions of the study were that dexrazosane may be safely associated with anthracyclines, in adult and young patients, in order to prevent subclinical and clinical heart failure.92

It was hypothesized that dexrazosane may have been responsible to induce acute myeloid leukaemia, so that it was not prescribed for children in Europe for some time. However, in a study of a large cohort of children treated with association of anthracyclines and dexrazosane, no significant increase in this type of cancer was observed and, to date, dexrazosane is the only recognized cardioprotective agent.93,92

Despite the above evidence, the American Society of Clinical Oncology recommends the use of this compound, in combination with doxorubicin 300 mg/m², only for adults suffering from metastatic breast cancer.94 Considering the fact that the action of dexrazosane is not able to prevent the left ventricular dysfunction in all the treated patients,90 the conclusions of a Cochrane library review were that the drug may slightly reduce the undesirable effects of cancer chemotherapy.92

Other tested cardioprotective agents tested were probucol, amifostine and N-acetilcisteine, but their effects, encouraging in vitro or in animal models, were not confirmed in humans.95–103

Medical treatment for cardiac insufficiency

Carvedilol

Carvedilol is a β-adrenergic antagonist widely administered for heart failure, hypertension and angina. It is an α, blocker which acts as a vasodilator, and also has an antioxidant action.104–106 Several studies showed that carvedilol and its metabolites can prevent lipid peroxidation and loss of endogenous antioxidants such as vitamin E and glutathione.106,107 The carvedilol-induced cardioprotection seems, therefore, be linked to the antioxidant effect, rather than its antiadrenergic properties.

In-vitro studies showed that carvedilol can inhibit apoptosis and reduce the production of superoxide anions and hydroperoxide.108 In some animal models, carvedilol reduced the incidence of doxorubicin-induced dilated cardiomyopathy, slowing the decline in left ventricular function, and attenuated symptoms.109,110 An insufficient activity of study was conducted in young patients.111
Renin-angiotensin-aldosterone system inhibition

Increasing evidence shows that the alteration of the renin-angiotensin-aldosterone system is involved in the anthracycline-induced CTX. Accordingly, antagonists of the angiotensin II receptor (such as valsartan and telmisartan) are effective in reducing myocardial damage in adult cancer patients, as well as certain ACE inhibitors (captopril and enalapril). Regrettably, it is unknown whether these positive and promising results may be reproduced in children as well. For instance, in a Cochrane Library review that focused on the possible cardioprotective effect of enalapril in the paediatric population, only one study was eligible. A reduction in LV dimensions was shown, but no clinic outcomes were reported. Rather, treatment with enalapril was associated with coughing, hypotension and fatigue.

Sildenafil

Sildenafil is an inhibitor of the enzyme phosphodiesterase-5 widely used not only to treat erectile dysfunction and pulmonary arterial hypertension, but also studied as cardioprotective agent during antiblastic chemotherapy. In the heart of rat, the combination of doxorubicin and sildenafil reduced the cell apoptosis and desmin bridges destruction, compared with the control animals treated with doxorubicin alone. Even the electrocardiogram showed a ST elevation tract or slowing down lower in the first group compared with the second. The sildenafil cardioprotective action against doxorubicin-induced CTX appears mediated by ATP-sensitive mitochondrial channels.

Although the pharmacokinetics of the drug in children has yet to be fully elucidated, these preliminary results, which resemble the effective treatment with sildenafil of pulmonary arterial hypertension in newborns and grown up congenital hearts, allow cautious optimism.

An alarm was recently raised about a possible detrimental effect of sildenafil in increasing immunosuppressive action of anthracyclines, as phosphodiesterase-5 is widely expressed in macrophages and other immune cells. This concern has been removed from the study of Di et al., which demonstrated that sildenafil, in combination with cisplatin, paclitaxel, camptothecin and doxorubicin neither reduces the antineoplastic efficiency, nor increases the immunosuppressive action of these compounds in human and mammalian breast cancer cellular cultures. It is unknown whether the cardioprotective effect of sildenafil is transient or persisting even against late CTX.

Adiponectin

Adiponectin is an adipocyte-derived hormone that, in an animal model, showed a cardioprotective action against doxorubicin. In detail, adiponectin was able to reduce the LV dilation and improve cardiac pump function in rats, through an antiapoptotic effect, activated by protein kinase upregulation, in turn activated by AMP. Moreover, it is unknown whether there is a possibility that these preliminary results, in the future, may be addressed to children.

Erythropoietin

Erythropoietin is a cytokine released by kidney and involved in haematopoiesis. The stimulation of cardiac receptors of erythropoietin would be beneficial in the improvement of LV function in ischemic adult patients, reducing the time of hospitalization. Li et al. in a murine model of cancer, administered erythropoietin in combination with anthracyclines, obtaining a significant reduction of LV diameters and improvement in contractility. This evidence of a cardioprotective effect of erythropoietin has no equivalent in human studies, in both adult and paediatric populations.

Conclusion

The CTX from anthracyclines among young people with cancer is a real challenge for cardiologists and oncologists, because of its high morbidity and mortality, which may occur even several years after treatment completion. Beside the moral obligation to prevent the risk of heart disease in children recovered from another severe illness, there is a social problem, concerning the increase of the Health System spending.

On this basis, the development of cardioprotective strategies is now mandatory in these subjects so young and vulnerable. Because of the lack of adequate scientific evidence, to date most of these strategies are based on clinical and therapeutic options borrowed from adults and extended in an arbitrary way to children and adolescents.

A hope of progress comes from the development of new promising technologies, such as the omic sciences, investigations of ROS-dependent pathways, and autologous cardiac stem and progenitor cells. The aim is to identify the anthracycline-induced alterations, prevent their cardiac side-effects, and implement more personalized treatments. There is an urgent need to fill this gap of knowledge, in order to identify and establish optimal prevention and management strategies that balance oncologic efficacy with long-term safety.

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