EUROPEAN JOURNAL OF CANCER 42 (2006) 3199–3205

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Anthracycline-induced cardiotoxicity: Comparison of recommendations for monitoring cardiac function during therapy in paediatric oncology trials

Elvira C. van Dalen, Marieke van den Brug, Huib N. Caron, Leontien C.M. Kremer*

Department of Paediatric Oncology, Room F8-257, Emma Children's Hospital/Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 26 April 2006
Received in revised form 19 July 2006
Accepted 2 August 2006
Available online 29 September 2006

Keywords:
Anthracyclines
Cardiotoxicity
Childhood cancer
Cardiac monitoring

ABSTRACT

The use of anthracyclines is limited by a dose-dependent cardiotoxicity (A-CT). The aim of this study was to gain insight in the currently available guidelines for monitoring cardiotoxicity during anthracycline therapy in children and in the monitoring recommendations currently used in European paediatric oncology trials. An extensive literature search to identify guidelines was performed and one guideline was identified. Twelve protocols including anthracycline therapy were evaluated.

With regard to the minimally required diagnostic tests, parameters and definitions of A-CT most protocols roughly followed the guideline. However, both monitoring schedules and recommendations to prevent further cardiac damage in case A-CT was diagnosed varied widely between protocols and only a minority of the protocols followed the recommendations of the guideline.

In conclusion, despite an existing guideline, there is a wide variation in the recommendations for monitoring cardiac function during anthracycline therapy in the currently used European paediatric oncology protocols. A possible explanation could be the lack of rigorous evidence on the most optimal way to monitor cardiac function in children treated with anthracyclines. There is a strong need for evidence from clinical research which can support recommendations for monitoring cardiac function during anthracycline therapy for childhood cancer. In the meantime, it is important to uniformise the used cardiac monitoring schedules.

1. Introduction

Anthracyclines have gained widespread use in the treatment of childhood malignancies: nearly 60% of children diagnosed with a malignancy receive anthracyclines. The introduction of anthracyclines has contributed to the improvement in survival rates of childhood cancer: from 30% in the 1960s to 70% nowadays.[1,2] As a result, a rapidly growing number of children will have survived childhood cancer. In the Netherlands, nowadays, approximately 1 out of every 750–800 young adults has survived childhood cancer.[3]

However, the use of anthracyclines is limited by a dose-dependent cardiotoxicity.[4] This cardiotoxicity can become manifest in patients as either clinical heart failure or asymptomatic heart damage, which encloses various cardiac abnormalities diagnosed with different diagnostic methods.

* *Corresponding author:* Tel.: +31 20 5665697; fax: +31 20 5669021.
E-mail address: e.c.vandalen@amc.uva.nl (E.C. van Dalen).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.08.002

According to the time of presentation, anthracycline-induced cardiotoxicity (A-CT) can be divided into early and late cardiotoxicity: early cardiotoxicity refers to heart damage that develops during anthracycline therapy or in the first year after its completion, and late cardiotoxicity manifests itself thereafter.[5]

Steinherz and colleagues published guidelines for cardiac monitoring of children treated with anthracyclines.[6] Serial monitoring of the cardiac function of children receiving anthracycline therapy allows early identification of heart damage. During therapy, the anthracycline dosage can then be adjusted or anthracycline therapy can be even stopped, which, hopefully, can prevent more cardiac damage to occur.

The aim of this study was to gain insight in the currently available guidelines for monitoring cardiotoxicity during anthracycline therapy in children and in the monitoring recommendations currently used in European paediatric oncology trials.

2. Materials and methods

2.1. Search strategy for identification of currently available guidelines for monitoring cardiotoxicity during anthracycline therapy in children

The objective of the literature search was to identify all published guidelines for monitoring cardiotoxicity during anthracycline therapy in children. The database of MEDLINE (from 1966 to April 2006) was searched, combining appropriate subject headings and textwords for anthracyclines, guidelines, children and cardiotoxicity (complete search strategy can be obtained from the corresponding author). In addition, we searched for relevant guidelines in the National Guideline Clearinghouse (www.guideline.gov), the Scottish Intercollegiate Guidelines Network (SIGN; www.sign.ac.uk) and the Children's Oncology Group (COG; www.childrensoncologygroup.org). No language restriction was imposed.

2.2. Currently used European paediatric oncology protocols

Collaborative European multicenter trial protocols in paediatric oncology including anthracycline therapy were evaluated. We included all appropriate protocols used in the paediatric oncology unit of our hospital on 1st January 2003.

For each study, the following information was recorded: (a) the tumour diagnosis; (b) the anthracycline derivate used; (c) the anthracycline dose (cumulative and per course); (d) the recommended test(s) for measuring cardiac function; (e) the recommended parameter(s) including the exact methods of the measurement of cardiac function; (f) recommended schedule for monitoring cardiotoxicity during therapy; (g) the used definition of values considered to be abnormal; (h) recommendations to prevent further deterioration of an abnormal cardiac function; and (i) radiotherapy involving the mediastinum.

In case of indistinctness, the local paediatric oncologist responsible for the protocol was contacted.

3. Results

3.1. Currently available guidelines for monitoring cardiotoxicity during anthracycline therapy in children

We identified one guideline for monitoring cardiotoxicity during anthracycline therapy in children published in 1992.[6] This guideline has been formulated on the basis of the existing literature, the established methods and norms for monitoring of cardiac function in children, and the experience in the institutions of the authors. The recommendations proposed in this guideline are summarized in Table 1.

Testing should be done sufficiently distant from the preceding anthracycline dose to avoid the transient myocardial depressant effects of the drug as well as the false hypercontractility from the catecholamine release which accompanies and follows administration of anthracyclines. Therefore, it is recommended to schedule testing at least 3 weeks after the last anthracycline dose and 1 week before the next dose. Testing should be performed, if possible, when the patient is normothermic and with haemoglobin maintained at or above 90 g/L.

3.2. Currently used European paediatric oncology protocols

3.2.1. Study characteristics

Twelve protocols were included in this study.[7–18]. Table 2 shows the characteristics of the individual protocols. Different anthracycline derivates were used for the treatment of various solid and haematological malignancies; the cumulative anthracycline dose varied between 15 mg/m^2 and 450 mg/m^2. All protocols provided recommendations for monitoring cardiac function (see Table 3).

3.2.2. Assessment of cardiac function

3.2.2.1. Diagnostic test(s). All evaluated protocols used the minimally required diagnostic tests as recommended in the guideline, i.e. echocardiography and/or radionuclide angiocardiography (MUGA-scan). Eleven protocols used echocardiography to measure cardiac function,[7–10,12–18] one study used either echocardiography or a MUGA-scan.[11] None of the studies used both tests in combination as recommended by the guideline. Furthermore, alongside echocardiography or MUGA-scan, in 1 study it was allowed to replace the baseline echocardiography by an other test of left ventricular function[10] and three studies used electrocardiography (ECG) at baseline.[11,15,17]

3.2.2.2. Parameters used to assess cardiac function. Eleven of the 12 protocols mentioned the used parameters to assess cardiac function (like for example the left ventricular shortening fraction (LVSF)) and these were also as minimally recommended by the guideline. Cardiac function was measured as the LVSF alone in six protocols,[7–9,13,14,17] four protocols used both the LVSF and the left ventricular ejection fraction (LVEF),[10,11,15,18] one protocol used the LVSF, LVEF and the end systolic wall stress (ESWS).[12]

Table 1 – Guidelines for monitoring cardiotoxicity during anthracycline therapy in children as proposed by Steinherz et al.[6]

Diagnostic test(s) Parameter(s)	Definition of anthra-cardiotoxicity	Monitoring schedule during therapy[a]	Recommendations to prevent further cardiac damage in case anthra-cardiotoxicity was diagnosed
Echocardiography and when available RNA[b] SF and EF	*Echocardiography:* SF <29% Drop in SF by an absolute value of ⩾10% *RNA:* *EF* < 55% Drop in EF by an absolute value of ⩾10% Decrease in EF with stress	Baseline <300 mg/m^2 (irrespective of RT): echo before every other course ⩾300 mg/m^2 and RT ⩽ 1000 cGy: echo before every course ⩾300 mg/m^2 and RT > 1000 cGy: echo and RNA before every course ⩾400 mg/m^2 (irrespective of RT): echo and RNA before every course All patients: echo 3–6 months after therapy[c]	When significant deterioration of both echo and RNA are confirmed by 2 sequential tests, a myocardial biopsy should be obtained if possible. Anthracyclines should be discontinued unless there is biopsy proof that excludes anthra-cardiotoxicity or, if biopsy is not obtained, if there is sustained recovery (2 tests a month apart) of both echo and RNA to normal limits. When deterioration of cardiac function is confirmed on echo or RNA and the other test remains normal, anthracyclines should be temporarily withheld while echo and RNA are repeated. If there is no further deterioration shown by either test, anthracyclines can be continued even though one test remains stably abnormal. If there is further deterioration shown by either test, anthracyclines should be discontinued. If only one of these tests is available and that shows a significant deterioration of function, anthracycline should be withheld until that test is repeated. A sustained deterioration below normal limits or progressive deterioration within normal limits necessitates discontinuation of anthracyclines, unless biopsy proves this is not due to anthracyclines.

RNA, radionuclide angiocardiography; SF, left ventricular shortening fraction; EF, left ventricular ejection fraction; anthra, anthracycline-induced; echo, echocardiography; RT, mediastinal radiotherapy.

a For treatment with doxorubicin and/or daunorubicin (for treatment with other agents: echocardiography and RNA prior to every course).

b At baseline also ECG.

c Unclear if also ECG at the end of therapy due to difference between text and table of the guideline.

3.2.2.3. *Methods of the echocardiographic measurement of cardiac function and the condition of the patient at the moment of the measurement*. Only two protocols provided some information about the exact method used to measure cardiac function.[9,12] In the SIOPEL-3 protocol, 2D and M-mode echocardiography should be performed when the patient is normothermic, has a normal haemoglobin and is not being hyperhydrated, which is in accordance with the guideline. In the SIOP-2001 protocol, the ESWS should be calculated with the given formula, which requires blood pressure measurements at time of Doppler US.

3.2.2.4. *Definition of anthracycline-induced cardiotoxicity*. A definition of A-CT was given in 11 protocols.[7–15,17,18] In 10 protocols, exact values considered to represent an abnormal cardiac function were reported, while the other protocol only mentioned significant falls in left ventricular function or signs of heart failure to be abnormal.[10] For the LVSF these values were roughly the same as used in the guideline (i.e. < 28 or 29%). For the LVEF, some protocols used values lower than the value used in the guideline.[11,15,18] In 4 of the 10 protocols[13–15,18] which provided exact values considered to represent an abnormal cardiac function, the definition of A-CT was based on 1 option, whereas in the other 6 protocols the definition of A-CT enclosed different possibilities.

3.2.3. *Monitoring schedules during therapy*

The recommended monitoring schedule varied between protocols. There was variation in both the frequency and timing of testing. Four protocols monitored patients at the time points described in the guideline.[7,13–15] Five protocols monitored patients less than recommended in the guideline,[9,11,12,16,18] one protocol monitored patients too often[10] and one protocol not always on the correct time point.[17] Finally, in one protocol, the exact time of cardiac monitoring was unclear: at one time it was stated that echocardiography should be performed prior to each dose of epirubicin, at another it was stated that this should be done prior to each alternate dose.[8] Since none of the protocols mentioned the exact dose of radiotherapy involving the mediastinum patients could receive, it was not possible to include radiotherapy in the assessment of the use of the guidelines in the different protocols.

Table 2 – Study characteristics of the 12 evaluated paediatric oncology trials

Protocol	Tumour	Anthra. derivate	Cum. anthra. dose (mg/m^2)/anthra. dose per course (mg/m^2)	RT involving (part of) the mediastinum (dose Gy)
MMT-95[7]	Soft tissue tumours	Epirubicin	150–450/150	Depending on tumour location: both lungs (15 Gy with lung correction); spinal cord (40 Gy), whole abdomen (25 Gy) or pleura (nm).
MMT-98 (stage IV)[8]	Soft tissue tumours	Epirubicin	150–450/150	See MMT-95.
SIOPEL-3[9]	Hepatoblastoma and hepatocellular carcinoma	Doxorubicin	300/60	Consider for lung metastases if no effect other therapy (dose nm).
EORTC 80931[10]	Osteosarcoma	Doxorubicin	450/75	Nm
Euro-E.W.I.N.G.99[11]	Ewing sarcoma	Doxorubicin	360/60	Depending on tumour location (max. 30 Gy).
SIOP 2001[12]	Nephroblastoma	Doxorubicin	250–300/50	Depending on tumour location: whole abdomen (21 Gy and boost; children <1 year: 10–12 Gy); lungs (15 Gy with tissue correction and boost). If possible no cardiac RT.
LMB-96[13]	B-cell lymphoma/leukaemia	Doxorubicin	120–240/60	No
ALCL-99[14]	Anaplastic lymphosarcoma	Doxorubicin	150/50	Nm
SNWLK-ANLL-97[15]	ANLL	Daunorubicin	300/150	TBI when BMT and >2 years (dose age-dependent: 7 to 12Gy).
SNWLK/DCOG-ALL-9 (HR)[16]	ALL	Daunorubicin	175/25	Nm
Interfant 99[17]	ALL in children < 1 year	Daunorubicin	180/30–60	Nm
SNWLK-ALL-recidief 98[18]	ALL (1^{st} recurrence)	Idarubicin	15–75/15	TBI when BMT and $\geqslant$2 years (dose age-dependent: 7–12 Gy); craniospinal (max. 24/15 Gy).

ANLL, acute non-lymphocytic leukaemia; ALL, acute lymphocytic leukaemia; anthra., anthracycline; cum., cumulative; RT, radiotherapy; nm, not mentioned; max., maximal; TBI, total body irradiation; BMT, bone marrow transplantation.

3.2.4. *Recommendations to prevent further cardiac damage*

Ten protocols provided recommendations to prevent further cardiac damage in case an abnormal cardiac function was diagnosed.[7–14,17,18] These recommendations varied widely, some protocols provided explicit instructions, whereas others for example only stated to consider dose modification in case of A-CT. Only three almost completely followed the guideline.[9,13,17] None of the protocols mentioned specific follow-up of patients in which cardiac damage was diagnosed to assess the effect of the provided recommendation on cardiac function and on for example tumour response.

4. Discussion

This study shows that the recommendations for monitoring cardiac function during anthracycline therapy varied widely in the 12 evaluated protocols of European paediatric oncology trials. All treatment protocols used echocardiographic measurements for monitoring cardiac function, as recommended in the published guideline by Steinherz and colleagues on cardiac monitoring of children during and after anthracycline therapy. None of the protocols advised radionuclide angiocardiography as the standard diagnostic test. Most protocols used parameters to assess cardiac function as recommended in the guideline (i.e. LVSF and/or LVEF) and the used definitions of A-CT were roughly the same as used in the guideline. However, only a minority of the protocols provided some information about the exact methods of the echocardiographic measurement of cardiac function and the condition of the patient at the time of the measurement.[6,19] Both monitoring schedules and recommendations to prevent further cardiac damage in case A-CT was diagnosed varied widely between protocols and only a minority of the protocols followed the recommendations of the guideline.

A possible explanation for this wide variation in cardiac screening could be the fact that, at the moment, there is no evidence on the most optimal way to monitor cardiac function in children treated with anthracyclines with regard to the diagnostic test(s), time and frequency of testing, and interventions based on the results.

Since the measurement of the echocardiographic LVSF is both non-invasive and available in most paediatric oncology centres, it is the most widely used diagnostic method for detecting cardiotoxicity in children. However, the echocardiographic LVSF has limitations. The value of the LVSF depends on the exact methods used to obtain the LVSF[19] and also on the condition of the patient at the moment of the measurement.[6] Moreover, the interpretation of the measurement of

Table 3 – Recommendations for monitoring cardiac function in the 12 evaluated paediatric oncology trials

Protocol	Diagnostic test(s) Parameter(s)	Definition of anthra-cardiotoxicity	Monitoring schedule during therapy	Recommendations to prevent further cardiac damage in case anthra-cardiotoxicity was diagnosed
MMT-95[7]	Echocardiography SF	SF <28% Reduction in SF of >10% between doses	Baseline, at 150 and 300 mg/m^2 End of therapy	Consider dose modification
MMT-98 (stage IV)[8]	Echocardiography SF	SF <28% Reduction in SF of >10% between doses	Baseline, at 150 and 300 mg/m^2 [a] End of therapy	Consider dose modification
SIOPEL-3[9]	Echocardiography SF	SF <29% or an absolute fall in SF by >10%	Baseline, and at 180 mg/m^2 End of therapy	SF < 29%: Stop doxorubicin, if subsequent testing shows an increase in SF, consider reintroduction Fall SF > 10%, but still >29%: Contact chemotherapy panel coordinator
EORTC 80931[10]	Echocardiography SF and EF	Significant falls in left ventricular function or signs of heart failure	Baseline, at 150, 225, 300 and 375 mg/m^2 End of therapy	Discuss with study coordinator
Euro-E.W.I.N.G.99[11]	Echocardiography or MUGA-scan SF and EF	SF < 29% EF < 40% $\geqslant$10% absolute decrease (if abnormal: repeat test after 7 days)	Baseline, at 240, and 300 mg/m^2 End of therapy	Stop doxorubicin
SIOP 2001[12]	Echocardiography SF, EF and ESWS	SF < 28% Reduction in SF of >10% between 2 administrations Reduction in SF of >20% from baseline (if abnormal: repeat test after 3 weeks)	Baseline and after every 200 mg/m^2	Consider dose modification
LMB-96[13]	Echocardiography SF	SF $\leqslant$28%	Baseline, and at 120 mg/m^2 End of therapy	Hold doxorubicin until SF $\geqslant$ 28%
ALCL-99[14]	Echocardiography SF	SF < 28% and other evidence of cardiac dysfunction	At least baseline, and after 100 mg/m^2 End of therapy	Discuss with study coordinator
SNWLK-ANLL-97[15]	Echocardiography SF and EF	SF < 28% EF <50%	Baseline End of therapy	Nm
SNWLK/DCOG-ALL-9 (HR)[16]	Echocardiography Nm	Nm	Baseline	Nm
Interfant 99[17]	Echocardiography SF	SF < 28% Drop in SF > 10%	Baseline, and at 60 and 150 mg/m^2 End of therapy	SF (repeatedly) <27%: Discontinue daunorubicin for this course SF 27–30% or higher: Normal daunorubicin dose
SNWLK-ALL-recidief 98[18]	Echocardiography SF and EF	SF <28% EF < 50%	Baseline, and at 15, 30, 45, and 60 mg/m^2	Discontinue idarubicin

SF, left ventricular shortening fraction; EF, left ventricular ejection fraction; MUGA, multiple gated acquisition scan; ESWS, end systolic wall stress; nm, not mentioned; anthra, anthracycline-induced.

a The exact time of cardiac monitoring was unclear.

the LVSF can vary considerably between different observers.[20] Also, no studies evaluated the predictive value of the echocardiographic LVSF as a surrogate marker for the future development of clinical heart failure after anthracycline therapy for childhood cancer[21] as was confirmed by an extensive literature search (complete search strategy can be obtained from the corresponding author).

Steinherz and colleagues[6] published guidelines for cardiac monitoring during anthracycline therapy in children treated with anthracyclines (see Table 1). They are criticized by Lipshultz and colleagues,[22] especially with regard to the potential risk of excess mortality of the proposed anthracycline dose modifications to prevent further cardiac damage. After an extensive literature search (complete search strategy can be obtained from the corresponding author), we were not able to identify any randomized studies evaluating the effects of dose modification based on cardiac test results and therefore any deviations from protocol are not based on experimental evidence. None of the evaluated protocols mentioned specific follow-up of patients in which cardiac damage was diagnosed to assess the effect of dose modifications on cardiac function and on tumour response.

There is a strong need for evidence from clinical research which can support recommendations for monitoring cardiac function during anthracycline therapy for childhood cancer. Unfortunately, this will be a time consuming process and a large number of patients needs to be included in these trials in order to obtain reliable evidence. In the meantime, we feel that it is very important to at least uniformise the used monitoring schedules in children treated with anthracyclines with regard to the diagnostic test(s), the exact methods of the echocardiographic measurement of cardiac function and the condition of the patient at the time of the measurement, and the time and frequency of testing. This is necessary for different reasons. First, since the cardiac function of all children treated with anthracyclines will then be monitored according to the same schedule, it will be much easier to implement in daily practice. Second, it is necessary to compare the results of studies evaluating A-CT in children. Clear information on the required patient conditions to assess cardiac function and the exact methods used to obtain the LVSF, will make it possible to compare the LVSF obtained in different centers. To uniformise the currently used monitoring schedules in European paediatric oncology trials including treatment with anthracyclines, we propose the organisation of a consensus meeting with experts in the field, preferable guided by SIOP Europe.

In conclusion, despite an existing guideline for monitoring cardiotoxicity during anthracycline therapy in children, there is a wide variation in the recommendations for monitoring cardiac function during anthracycline therapy in the protocols of European paediatric oncology trials currently used. A possible explanation could be the lack of rigorous evidence on the most optimal way to monitor cardiac function in children treated with anthracyclines. There is a strong need for evidence from clinical research which can support recommendations for monitoring cardiac function during anthracycline therapy for childhood cancer. In the meantime, it is important to uniformise the used cardiac monitoring schedules.

Conflict of interest statement

None of the authors have competing interests.

Acknowledgements

We thank the paediatric oncologists of the Emma Children's Hospital who provided information in case indistinctness was identified in a protocol. We also thank Nelia Langeveld for providing the protocols. This study was funded by Paediatric Cancer Research (SKK), Amsterdam, the Netherlands.

REFERENCES

1. Heymans HS, Caron HN. Childhood cancers in the Netherlands (1989–1997). *Ned Tijdschr Geneesk* 2001;**145**:1442–4.
2. Gatta G, Capocaccia R, Coleman MP, Ries LA, Berrino F. Childhood cancer survival in Europe and the United States. *Cancer* 2002;**95**:1767–72.
3. Heikens J. Childhood cancer and the price of cure: studies on late effects of childhood cancer treatment. Thesis, University of Amsterdam, Amsterdam; 2000.
4. Bonadonna G, Monfardini S. Cardiac toxicity of daunorubicin. *Lancet* 1969;**1**:837.
5. Shan K, Lincoff AM, Young JB. Anthracycline-induced cardiotoxicity. *Ann Intern Med* 1996;**125**:47–58.
6. Steinherz LJ, Graham T, Hurwitz R, et al. Guidelines for cardiac monitoring of children during and after anthracycline therapy: report of the cardiology committee of the Children's Cancer Study Group. *Pediatrics* 1992;**89**:942–9.
7. MMT-95 study for rhabdomyosarcoma and other malignant soft tissue tumours of childhood. UKCCSG data centre, version May 1995.
8. MMT-98 study for metastatic disease: rhabdomyosarcoma and other malignant soft tissue sarcoma of childhood. UKCCSG data centre, version August 1998.
9. SIOPEL 3 Liver tumour studies. Version May 1998.
10. EORTC 80931 protocol MRC BO06 European osteosarcoma intergroup: a randomized trial of chemotherapy using doxorubicin plus cisplatin at standard or increased dose-intensity (± granulocyte colony-stimulating factor) in the treatment of patients with operable osteosarcoma.
11. EURO-E.W.I.N.G.99 (European Ewing Tumor Working Initiative of National groups). Ewing tumour studies 1999. UKCCSG data centre, version 1999-9-27.
12. SIOP-2001 nephroblastoma clinical trial and study. Protocol December 2001.
13. FAB LMB-96. Treatment of mature B-cell lymphoma/leukaemia, a SFOP LMB 96/CCG 5961/UKCCSG NHL 9600 cooperative study. Amended 27 February 1997.
14. ALCL-99 International protocol for the treatment of childhood anaplastic large cell lymphoma. Version 11-4-00.
15. MRC-AML 12/SNWLK-ANLL-97 Diagnostiek en behandeling van kinderen met acute niet-lymfatische leukemie (ANLL).
16. SNWLK/DCOG-ALL-9. Protocol for treatment and research of acute lymphoblastic leukaemia of childhood of the Dutch Childhood Oncology Group (formerly Stichting Nederlandse Werkgroep Leukemie bij Kinderen, SNWLK).
17. Interfant-99. International collaborative treatment protocol for infants under one year with acute lymphoblastic leukemia.

18. SNWLK-ALL-recidief 98. Diagnostiek en behandeling van kinderen met eerste recidief acute lymfatische leukemie.
19. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978;**58**:1072–83.
20. Lipshultz SE, Easley KA, Orav J, et al. Reliability of multicenter pediatric echocardiographic measurements of left ventricular structure and function: the prospective P(2)C(2) HIV study. *Circulation* 2001;**104**:310–6.
21. Lipshultz SE, Colan SD. Cardiovascular trials in long-term survivors of childhood cancer. *J Clin Oncol* 2004;**22**:769–73.
22. Lipshultz S, Sanders S, Goorin A, Krischer JP, Sallan SE, Colan SD. Monitoring for anthracycline cardiotoxicity. *Pediatrics* 1994;**93**:433–7.