The duration of anthracycline infusion should be at least one hour in children with cancer

Loeffen, Erik A. H.; van Dalen, Elvira C.; Mulder, Renee L.; van de Wetering, Marianne D.; Kremer, Leontien C. M.; Tissing, Wim J. E.; Anthracycline Cardiotoxicity Working Group

Published in:
Pediatric blood & cancer

DOI:
10.1002/pbc.26867

Publication date:
2018

Received: 7 August 2017 | Revised: 25 September 2017 | Accepted: 26 September 2017

DOI: 10.1002/pbc.26867

CLINICAL PRACTICE GUIDELINES

WILEY Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

The duration of anthracycline infusion should be at least one hour in children with cancer: A clinical practice guideline

Erik A.H. Loeffen[1] | **Elvira C. van Dalen**[2] | **Renée L. Mulder**[2] | **Marianne D. van de Wetering**[2] | **Leontien C.M. Kremer**[2†] | **Wim J.E. Tissing**[1†] | **on behalf of the Anthracycline Cardiotoxicity Working Group***

[1]University of Groningen, University Medical Center Groningen, Beatrix Children's Hospital, Department of Pediatric Oncology, Groningen, The Netherlands

[2]Department of Pediatric Oncology, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands

Correspondence
Erik A.H. Loeffen, Department of Pediatric Oncology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands.
Email: eah.loeffen@umcg.nl

*Collaborators (alphabetical order): Floor C.H. Abbink (pediatric oncologist, VU Medical Center, Amsterdam, The Netherlands), Lynne M. Ball (pediatric oncologist, Leiden University Medical Center, Leiden, The Netherlands), Roger J.M. Brüggemann (clinical pharmacist, Radboud University Medical Center, Nijmegen, The Netherlands), Annelies M.C. Mavinkurve-Groothuis (pediatric oncologist, Princess Máxima Center, Utrecht, The Netherlands), Erna M.C. Michiels (pediatric oncologist, ErasmusMC/Sophia Children's Hospital, Rotterdam, The Netherlands), Heleen van der Pal (oncologist specialized in childhood cancer late effects, Academic Medical Center, Amsterdam, The Netherlands), Martijn G. Slieker (pediatric cardiologist, Radboud University Medical Center, Nijmegen, The Netherlands).

†Leontien C.M. Kremer and Wim J.E. Tissing contributed equally to this work.

Funding information
Grant sponsor: Alpe d'HuZes foundation/Dutch Cancer Society (RUG 2013-6345); Grant sponsor: Stichting Kinderen Kankervrij (KiKa)

Abstract

We aimed to provide recommendations on the infusion duration of anthracycline chemotherapy agents in children with cancer. This study also serves as a practice example of the essential steps that need to be taken when using a previously published systematic review to develop a high-quality clinical practice guideline. Although evidence was scarce and included adult studies, the panel was able (using the Grading of Recommendations Assessment, Development and Evaluation evidence-to-decision framework) to recommend in favor of an anthracycline infusion duration of at least 1 hr (strong recommendation, very low to moderate quality of evidence). Recommending a precise optimal prolonged infusion duration was currently not possible.

KEYWORDS
anthracyclines, cardiotoxicity, chemotherapy, guideline, pediatric oncology, supportive care

1 | INTRODUCTION

Anthracycline chemotherapy agents are widely used in the treatment of various types of solid and hematologic childhood malignancies. A well-known and potentially severe side effect of this class of chemotherapeutic agents is cardiotoxicity.[1,2] More than 1 in every 20 children who receive 300 mg/m^2 anthracycline therapy for childhood cancer will develop clinical heart failure in the 20 years after treatment.[3] Subclinical cardiac dysfunction is even more prevalent, with studies reporting occurrence of subclinical cardiac dysfunction after anthracycline therapy in more than half of healthy survivors of childhood cancer.[4,5] As children have a long life expectancy when they are cured, these cardiotoxic effects imply a serious burden of disease.

To reduce the cardiotoxicity, various strategies have been studied. These comprise (1) change of agents, that is, different anthracycline derivates or omission of anthracyclines altogether, (2) administration of cardioprotective agents, or (3) change of anthracycline dosage

Abbreviations: CPG, clinical practice guideline; EtD, evidence to decision; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PICO, Patient Intervention Control Outcome; RR, relative risk

schedules.[6–12] The latter can be subdivided into a reduction of the dose or a prolongation of the infusion time.

The rationale of extending the infusion duration for avoiding anthracycline cardiotoxicity relies mainly on a longer but lower peak anthracycline dose. An important question is what effects this will have on the primary effect of anthracyclines, that is, the antitumor efficacy, and on other side effects such as nausea, alopecia, bone marrow depression, and natural cardiotoxicity.

At this moment, there is no clinical practice guideline (CPG) that provides recommendations regarding infusion duration of anthracycline chemotherapy in children. With this document, we aim to provide clinicians with an overview of the current evidence and to offer guidance with regard to infusion duration of anthracycline chemotherapy in children with cancer. Also we aim to show how a published systematic review can be used in developing a high-quality CPG, as there are several essential steps that need to be taken before recommendations can be formulated.

2 | METHODS

More extensive details regarding the methodology can be found in Supplementary Material S1.

2.1 | Guideline development panel

A multidisciplinary panel was formed, comprising Dutch individuals from all relevant fields. In total, the panel consisted of 15 members: two parent representatives from a national childhood cancer foundation, six pediatric oncologists, an oncologist (specialized in childhood cancer late effects), a pediatric cardiologist, a clinical pharmacist, three epidemiologists/guideline specialists, and a PhD student. Three of them were also authors of a 2016 Cochrane review on anthracycline chemotherapy infusion duration in cancer patients.[12] The parent representatives were not involved in the identification and appraisal of evidence, as this required specific (medical) knowledge. They did, however, receive a short guideline development training and were then involved in the processes of defining the hierarchy of outcomes, completing the evidence to decision (EtD) frameworks and formulating the recommendations. Their input and votes were weighed in a similar fashion as those by the care professionals involved.

2.2 | Clinical question

The central Patient-Intervention-Control-Outcome (PICO) question in this CPG was What is the effect on cardiotoxicity, that is, clinical and subclinical heart failure, and what are the other effects, that is, tumor response, progression-free survival, overall survival, adverse effects other than cardiac damage, and quality of life, (O) of a prolonged infusion duration of anthracycline chemotherapy (I) compared to a shorter infusion duration of anthracycline chemotherapy (C), in children with cancer (P)? The central PICO was divided into two PICOs, the first focusing on a push infusion (comparison of a ≥1 hr infusion duration with a push infusion, the latter defined as an infusion duration shorter than 1 hr), the second focusing on establishing a more specific prolonged infusion time (comparison of a ≥6 hr vs. a 1–6 hr infusion duration, similar to the main question in the Cochrane review).[12]

2.3 | Evidence search, selection, and appraisal

The Cochrane review was the starting point for the evidence search.[12] In an update search, we searched the electronic databases of MEDLINE/PubMed and EMBASE/Ovid, and the International Standard Randomised Controlled Trial Number registry for ongoing trials. After dual evidence selection, the evidence was appraised and summarized in comprehensive evidence summaries. For quality appraisal, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used.[13,14]

2.4 | From evidence to recommendations

During an in-person group meeting, several steps were undertaken in the process of formulating the recommendations in accordance with the GRADE method.[15] Most importantly, the hierarchy of the outcomes was defined and for each PICO an EtD frameworks was completed. The EtD framework provides a systematic and transparent approach to formulating healthcare recommendations. From the EtD frameworks, overall conclusions were formulated, from which the recommendations were derived. All final recommendations had to be supported unanimously.

Decisions were taken through group discussion and consensus. In all steps, but the formulation of final recommendations, a voting procedure was performed (majority voting system) in case of absence of unanimity.

3 | RESULTS

In the search update, 152 citations were retrieved. No new relevant studies were identified that were not already included in the Cochrane review.

3.1 | Included studies

In all, seven studies were included.[11] Three studies comprised only children (n = 343), of which long-term follow-up data were published for one study (n = 92).[7,16–18] Four studies (n = 436) were categorized as adult studies.[19–22]

3.2 | Description of the evidence

See also Tables 1–3 for a full description of the evidence per PICO (an evidence table for adult studies regarding ≥6 hr versus 1–6 hr anthracycline infusion duration was not prepared, since no adult studies were included for this question).

For the first PICO (≥1 hr vs. push infusion), four adult studies (n = 436) and two pediatric studies (n = 165) were included (Tables 1 and 2). Most importantly, regarding clinical heart failure, in a

TABLE 1 PICO 1 ≥1 hr versus push, evidence table for pediatric studies that examined this question

Outcome	Number of studies	Number of participants	Follow up (median, range)	Anthracycline, cumulative dose in mg/m^2 (median), infusion times	Events	Statistical method	Effect size	Quality of evidence
(1) Clinical heart failure	1[7]	121	1.5 years, 0–4.7 years[a]	Doxorubicin, 340 versus 336, 48 hr versus less than 1 hr ("basically within 15 min")	0/57 versus 0/64	Risk ratio (95% CI)	Not estimable	⊕⊕◯◯ LOW[d]
(2) (Sub)clinical heart failure combined	0							
(3) Subclinical cardiac dysfunction as a continuous outcome	2 (pooling not possible)[7,18]	(1) 44 (2) 121	(1) 54+ months (minimal 25+ months) (2) 1.5 years, 0–4.7 years[a]	(1) Daunorubicin, 400 versus 360, 48 hr versus push (2) Doxorubicin, 340 versus 336, 48 hr versus less than 1 hr ("basically within 15 min")	(1) Median change in LVSF +1 versus −6.5 (2) multiple median z-scores[b]	(1) nm (2) nm	(1) Significance not stated (2) Not significant	⊕⊕◯◯ LOW[e]
(4) Response rate	0							
(5) Overall survival	0[c]							
(6) Adverse effects other than cardiac damage	0							
(7) Quality of life	0							

[a]In this study, long-term follow-up data were published in 2012; *n* = 92, follow-up median 8 years (range: 3–13 years): between continuous arm (48 hr) or bolus arm (within 15 min) no differences in survival, LV echocardiographic characteristics, and LV structure and function were detected; also no clinical cardiac disease was detected in any patient. Conclusion: "Continuous infusion of doxorubicin and other anthracyclines is currently included in pediatric treatment protocols on the basis of results from short-term studies of adults that suggest continuous anthracycline infusion is cardioprotective. Given that we found no difference in cardioprotection between continuous and bolus doxorubicin administration, and there was no difference in ALL event-free survival between the two arms, we encourage pediatric oncology providers treating children with high-risk ALL to minimize or eliminate the use of continuous anthracycline infusion."

[b]Only a small percentage of the randomized participants were evaluated for this outcome (21–26%). Median Z score of different echocardiographic parameters (continuous infusion group vs. bolus group): diastolic dimension −0.23 versus −0.12, wall thickness −0.28 versus −0.32, systolic dimension 0.38 versus 0.85), left ventricular shortening fraction −1.77 versus −2.34, and mass −0.47 versus −0.65.

[c]One pediatric study[7] (n = 121) evaluated event-free survival (EFS); median follow up was 1.5 years (range: 0–4.7 years); EFS was 87.3% in the group with an infusion time of 48 hr versus 89% in the group with an infusion time of less than 1 hr ("basically within 15 min"); difference was not significant ($P = 0.50$). Quality of evidence = LOW[4].

[d]GRADE quality assessment[7] = study design is randomized trials, inconsistency and indirectness not serious, downgraded two levels because of serious risk of imprecision (neither criterion for precision is met) and serious risk of bias (random sequence generation (selection bias) unclear, allocation concealment (selection bias) low, performance bias high, detection bias unclear, attrition bias high, reporting bias high, other bias unclear); other considerations none.

[e]GRADE quality assessment[7,18] = study design is randomized trials, inconsistency and indirectness not serious, downgraded two levels because of serious risk of imprecision (neither criterion for precision is met) and serious risk of bias (random sequence generation (selection bias) unclear in 2/2, allocation concealment (selection bias) unclear in 1/2, low in 1/2, performance bias unclear in 1/2, high in 1/2, detection bias unclear in 2/2, attrition bias low in 1/2, high in 1/2, reporting bias high in 2/2, other bias unclear in 2/2); other considerations none.

meta-analysis of four adult studies (n = 436, 23 cases of heart failure), an infusion duration of ≥1 hr (vs. a push infusion) was associated with a significant lower rate of clinical heart failure. Focusing on clinical heart failure in pediatric studies (one study, n = 121), no cases of clinical heart failure were reported. For subclinical cardiac dysfunction, mixed results were found. For tumor response (two included adult studies), overall survival (two included adult studies), and adverse effects (one included adult study), no significant differences were found.

For the second PICO (≥6 hr vs. 1–6 hr infusion duration), no adult studies and one pediatric study (n = 178) were included (Table 3). In the included pediatric study, there were no cases reported for both clinical and subclinical heart. This study also reported on response rate, in which no significant difference was identified (within the follow-up time of only 7 days).

3.3 | Appraisal of the evidence

For all outcomes for which data were available, the quality of evidence ranged from very low to moderate. As only randomized controlled trials were included, the initial quality of evidence was regarded as high. However, due to serious risk of imprecision and serious risk of bias, outcomes for pediatric studies were downgraded two levels. Quality of evidence for all outcomes of adult studies was downgraded two

TABLE 2 PICO 1 ≥1 hr versus push, evidence table for adult studies that examined this question

Outcome	Number of studies	Number of participants	Follow up (median, range)	Anthracycline, cumulative dose infusion times	Events	Statistical method	Effect size	Quality of evidence
(1) Clinical heart failure	4 [19–22]	(1) 82 (2) 52 (3) 62 (4) 240	(1) 50 months*, nm (2) nm (3) nm (4) nm	(1) Doxorubicin, nm versus 420, 72 hr versus 5–10 min (2) Epirubicin, 630 versus 540, 48 hr versus 15 min (3) Doxorubicin, 428 versus 410, 6 hr versus 15–20 min (4) Doxorubicin, 221 versus 240, 96 hr versus bolus	(1) 2/43 versus 2/39 (2) 1/27 versus 3/25 (3) 0/31 versus 4/31 (4) 1/122 versus 10/118 Total = 4/223 versus 19/213	Risk ratio (95% CI)	Total 0.27 (0.09–0.81)	⊕⊕⊕○ MODERATE[a]
(2) (Sub)clinical heart failure combined, defined as:								
(2.1) ≥ 10% decrease in LVEF	1[21]	82	50 months*, nm	Doxorubicin, nm versus 420, 72 hr versus 5–10 min	16/43 versus 19/39	Risk ratio (95% CI)	0.76 (0.46–1.26)	⊕○○○ VERY LOW[b]
(2.2) ≥ 15% decrease in LVEF	1[20]	52	nm	Epirubicin, 630 versus 540, 48 hr versus 15 min	1/27 versus 3/25	Risk ratio (95% CI)	0.31 (0.03–2.78)	⊕⊕○○ LOW[c]
(2.3) a fall in LVEF of > 20%	1[22]	62	nm	Doxorubicin, 428 versus 410, 6 hr versus 15–20 min	0/31 versus 13/31	Risk ratio (95% CI)	0.04 (0.00–0.60)	⊕⊕⊕○ MODERATE[d]
(2.4) A decrease in LVEF	1[19]	240	nm	Doxorubicin, 221 versus 240, 96 hr versus bolus	6/122 versus 16/118	Risk ratio (95% CI)	0.36 (0.15–0.90)	⊕⊕⊕○ MODERATE[e]
(3) Subclinical heart failure as a continuous outcome	1[22]	62	nm	Doxorubicin, 428 versus 410, 6 hr versus 15–20 min	Mean fall in LVEF = 4% versus 17% and 6% versus 21%**	Wilcoxon signed-rank test	$P < 0.001$ (for both doses)	⊕⊕○○ LOW[f]
(4) Response rate***	2[19,20]	(1) 52 (2) 240	(1) nm (2) nm	(1) Epirubicin, 630 versus 540, 48 h versus 15 min (2) Doxorubicin, 221 versus 240, 96 hr versus bolus	1) 7/27 versus 3/25 2) 21/122 versus 20/118 Total = 28/149 versus 23/143	Risk ratio (95% CI)	Total 1.20 (0.65–2.22)	⊕○○○ VERY LOW[g]
(5) Overall survival	2[19,21]	(1) 82 (2) 240	(1) 50 months, nm (2) nm	(1) Doxorubicin, nm versus 420, 72 h versus 5–10 min 2) doxorubicin, 221 versus 240, 96 hr versus bolus	1) nm 2) nm	Hazard ratio (95% CI)	1.42 (0.61–3.30)	⊕○○○ VERY LOW[h]
(6) Adverse effects other than cardiac damage****	1[22]	62	nm	Doxorubicin, 428 versus 410, 6 hr versus 15–20 min	0/31 versus 1/31	Risk ratio (95% CI)	3.00, (0.13–70.92)	⊕⊕○○ LOW[i]

(Continues)

TABLE 2 (Continued)

Outcome	Number of studies	Number of participants	Follow up (median, range)	Anthracycline, cumulative dose infusion times	Events	Statistical method	Effect size	Quality of evidence
(7) Quality of life	0							

*This is the median follow up for surviving patients only.

**4% versus 17% is in the group with a cumulative anthracycline dose of 300 mg/m^2, and 6% versus 21% is in the group with a cumulative anthracycline dose of 400 mg/m^2.

***Event is defined as complete or partial remission.

****One included study, which included fatal sepsis as the only adverse effect studied.

[a]GRADE quality assessment[19,20,21,22] = study design is randomized trials, inconsistency not serious, downgraded two levels because of indirectness (adult population) and serious risk of bias (random sequence generation (selection bias) unclear in 3/4, high in 1/4, allocation concealment (selection bias) unclear in 2/4, high in 1/4, low in 1/4, performance bias unclear in 4/4, detection bias unclear in 4/4, attrition bias high in 1/4, low in 3/4, reporting bias high in 2/4, low in 2/4, other bias unclear in 3/4, high in 1/4); other considerations none, upgraded one level for large magnitude of effect (relative risk [RR] < 0.5; although the evidence is not direct, the panel felt that because the level of evidence is already downgraded for indirectness, upgrading for large magnitude of effect is justifiable).

[b]GRADE quality assessment[21] = study design is randomized trials, inconsistency not serious, downgraded three levels because of serious risk of imprecision (CI includes both a 25% benefit (RR 0.75) and a 25% harm (RR 1.25)), indirectness (adult population) and serious risk of bias (random sequence generation (selection bias) unclear, allocation concealment (selection bias) unclear, performance bias unclear, detection bias unclear, attrition bias high, reporting bias low, other bias unclear); other considerations none.

[c]GRADE quality assessment[20] = study design is randomized trials, inconsistency not serious, downgraded three levels because of serious risk of imprecision (CI includes both a 25% benefit (RR 0.75) and a 25% harm (RR1.25)), indirectness (adult population) and serious risk of bias (random sequence generation (selection bias) unclear, allocation concealment (selection bias) unclear, performance bias unclear, detection bias unclear, attrition bias low, reporting bias high, other bias high); other considerations none, upgraded one level for large magnitude of effect (RR < 0.5; although the evidence is not direct, the panel felt that because the level of evidence is already downgraded for indirectness, upgrading for large magnitude of effect is justifiable).

[d]GRADE Quality assessment[22] = study design is randomized trials, inconsistency not serious, downgraded two levels because of indirectness (adult population) and serious risk of bias (random sequence generation (selection bias) high, allocation concealment (selection bias) high, performance bias unclear, detection bias unclear, attrition bias low, reporting bias high, other bias unclear); other considerations none, upgraded one level for large magnitude of effect (RR < 0.5; although the evidence is not direct, the panel felt that because the level of evidence is already downgraded for indirectness, upgrading for large magnitude of effect is justifiable).

[e]GRADE quality assessment[19] = study design is randomized trials, inconsistency not serious, downgraded two levels because of indirectness (adult population) and serious risk of bias (random sequence generation (selection bias) unclear, allocation concealment (selection bias) low, performance bias unclear, detection bias unclear, attrition bias low, reporting bias low, other bias unclear), other considerations none, upgraded one level for large magnitude of effect (RR < 0.5; although the evidence is not direct, the panel felt that because the level of evidence is already downgraded for indirectness, upgrading for large magnitude of effect is justifiable).

[f]GRADE quality assessment[22] = study design is randomized trials, inconsistency not serious, downgraded two levels because of indirectness (adult population) and serious risk of bias (random sequence generation (selection bias) high, allocation concealment (selection bias) high, performance bias unclear, detection bias unclear, attrition bias low, reporting bias high, other bias unclear); other considerations none.

[g]GRADE quality assessment[19,20] = study design is randomized trials, inconsistency not serious, downgraded three levels because of serious risk of imprecision (CI includes both a 25% benefit (RR 0.75) and a 25% harm (RR 1.25)), indirectness (adult population) and serious risk of bias (random sequence generation (selection bias) unclear in 2/2, allocation concealment (selection bias) unclear in 1/2, low in 1/2, performance bias unclear in 2/2, detection bias unclear in 2/2, attrition bias low in 2/2, reporting bias low in 2/2, other bias high in 1/2, low in 1/2); other considerations none.

[h]GRADE quality assessment[19,21] = study design is randomized trials, inconsistency not serious, downgraded three levels because of serious risk of imprecision (CI includes both a 25% benefit (RR 0.75) and a 25% harm (RR 1.25)), indirectness (adult population) and serious risk of bias (random sequence generation (selection bias) unclear in 2/2, allocation concealment (selection bias) unclear in 1/2, low in 1/2, performance bias unclear in 2/2, detection bias low in 2/2, attrition bias unclear in 1/2, low in 1/2, reporting bias low in 2/2, other bias unclear in 2/2); other considerations none.

[i]GRADE quality assessment[22] = study design is randomized trials, inconsistency not serious, downgraded three levels because of serious risk of imprecision (CI includes both a 25% benefit (RR 0.75) and a 25% harm (RR1.25)), indirectness (adult population) and serious risk of bias (random sequence generation (selection bias) high, allocation concealment (selection bias) high, performance bias unclear, detection bias unclear, attrition bias low, reporting bias high, other bias unclear); other considerations none; upgraded one level for large magnitude of effect (RR > 2.0; although the evidence is not direct, the panel felt that because the level of evidence is already downgraded for indirectness, upgrading for large magnitude of effect is justifiable).

levels for indirectness and serious risk of bias. In addition, outcomes that met neither criterion for precision were downgraded another level for imprecision. The quality of evidence in five adult outcomes was upgraded one level for large magnitude of effect.

3.4 | From evidence to recommendations

Outcomes were unanimously categorized with respect to importance for decision making; overall survival, clinical heart failure, progression-free survival, and subclinical cardiac dysfunction were regarded as critical for decision making, and adverse effects other than cardiac damage, quality of life, tumor response, and costs were regarded as important, but not critical for decision making.

In Table 4, the overall conclusions from the completed EtD frameworks are shown (the entire completed EtD frameworks are available in Supplementary Material S2).

Regarding PICO 1 (≥1 hr vs. push infusion), the problem was regarded a priority and the overall certainty of the evidence was very low to moderate. The desirable anticipated effects were probably large and the undesirable effects were uncertain. The resources required were expected to be probably not small, but the option was considered both acceptable for key stake holders and feasible to implement.

TABLE 3 PICO 2 ≥6 hr versus 1–6 hr, evidence table for pediatric studies that examined this question

Outcome	Number of studies	Number of participants	Follow up (median, range)	Anthracycline, cumulative dose infusion times	Events	Statistical method	Effect size	Quality of evidence
(1) Clinical heart failure	1[16]	178	7 days	Daunorubicin, 36 versus 36, 24 hr versus 1 hr	0/93 versus 0/85	Risk ratio (95% CI)	Not estimable	⊕⊕◯◯ LOW[a]
(2) (Sub)clinical heart failure combined	1[16]	178	7 days[b]	Daunorubicin, 36 versus 36, 24 hr versus 1 hr	0/93 versus 0/85	Risk ratio (95% CI)	Not estimable	⊕⊕◯◯ LOW[a]
(3) Subclinical cardiac dysfunction as a continuous outcome	0							
(4) Response rate[c]	1[16]	178	7 days	Daunorubicin, 36 versus 36, 24 hr versus 1 hr	51/93 versus 38/85	Risk ratio (95% CI)	1.23, 95% CI 0.91–1.66	⊕⊕◯◯ LOW[a]
(5) Overall survival	0							
(6) Adverse effects other than cardiac damage	0							
(7) Quality of life	0							

[a]GRADE quality assessment[16] = study design is randomized trials, inconsistency and indirectness not serious, downgraded two levels because of serious risk of imprecision (neither criterion for precision is met) and serious risk of bias (random sequence generation (selection bias) unclear, allocation concealment (selection bias) unclear, performance bias unclear, detection bias unclear, attrition bias high, reporting bias high, other bias unclear); other considerations none.

[b]Study performed between 1992 and 1994, article published in 2007, stating: "No specific analysis of toxicity was performed in this study. However, evaluation of the regular documentation form of the COALL study did not show more mucositis in the long-term infusion group. This form also asks for signs of cardiac insufficiency. So far no patient in the randomized DNR infusion groups was reported to have developed clinical signs of cardiac insufficiency or decrease in shortening fraction below 25%."

[c]Event is defined as good response.

In all, the panel felt that the desirable consequences (of a ≥1 hr infusion duration vs. a push infusion) probably outweigh the undesirable consequences in most settings. Due to the large effect on particularly clinical heart failure in the adult studies, the panel was unanimous to make a strong recommendation in favor of an infusion duration of 1 hr or longer.

Regarding PICO 2 (≥6 hr vs. 1–6 hr), the problem was regarded a priority and the overall certainty of the evidence was low. Due to the very limited available evidence base and the uncertainty regarding the effects, no recommendation regarding favorability of an anthracycline infusion duration of 6 hr or more versus between 1 and 6 hr was possible.

Therefore, the question regarding optimal prolonged anthracycline infusion duration remains. Nevertheless, pediatric oncologists and policy makers have to make a decision on what infusion time to implement. The panel felt that clinicians can continue with their current practice when this is not a push infusion (i.e., shorter than 1 hr). Use of resources and (local) uniformity of care might be reasons to change this infusion duration.

To be able to further specify the infusion period in the future, the panel formulated a research recommendation for a large randomized controlled trial aiming to explore optimal infusion times of anthracycline chemotherapy in children with cancer (Table 5). Also, the panel felt there is an urge to undertake anthracycline pharmacokinetic studies in children with cancer to help generate knowledge regarding optimal infusion duration.

4 | DISCUSSION

In this guideline effort, we aimed to develop recommendations for the infusion duration of anthracycline chemotherapy and its effect on cardiotoxicity in children with cancer. In the end, the panel was not able to recommend a specific prolonged infusion duration; however, a recommendation in favor of an infusion duration ≥1 hr (compared to a push infusion) was composed (strong recommendation, very low to moderate quality evidence). In addition, the need for a large, randomized trial exploring optimal infusion duration and for specific anthracycline pharmacokinetic studies in children was also expressed by the guideline panel.

There are various approaches to CPG development, in which a systematic review should always play a pivotal role. One can perform this

TABLE 4 Overall conclusions and recommendations from the evidence to decision frameworks

PICO 1— infusion duration of anthracycline chemotherapy: 1 hr or more versus push infusion				
Undesirable consequences *clearly outweigh* desirable consequence in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ■	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐
We recommend against offering this option ☐	We suggest not offering this option ☐	We suggest offering this option ☐	We recommend offering this option ■	
Recommendation (text)	We recommend an infusion duration of 1 hr or more for anthracycline chemotherapy in children with cancer (strong recommendation, very low quality evidence)			
Justification	The evidence has an overall very low confidence, for some outcomes (among which the critical outcome clinical heart failure) this confidence is moderate. The evidence of moderate quality shows that there is a significant reduction in clinical heart failure (risk ratio 0.27, 95% CI = 0.09–0.81). According to these results supplemented with the expert knowledge represented in the panel, the panel felt that, although the undesirable consequences are still uncertain, the option of prolonged infusion probably outweighs the option of a push infusion. Given the large magnitude of effect on clinical heart failure, the panel was unanimous to make a strong recommendation in favor of an infusion duration of 1 hr or longer.			
Subgroup considerations	None described.			
Implementation considerations	As the panel was not able to make a recommendation other than a strong recommendation (based on very low to moderate quality evidence) in favor of an infusion duration of 1 hr or longer, it seems logical for centers who do not do a push (i.e., < 1 hr) infusion to either continue with their current approach or to uniform their approach with other adjacent centers.			
Monitoring and evaluation	None described.			
Research priorities	The panel felt a large randomized controlled trial is needed to explore optimal infusion times of anthracycline chemotherapy in children with cancer. Randomizing patients among two groups with an infusion duration of 1 hr versus 6 hr, taking into account overall survival, clinical heart failure, subclinical cardiac dysfunction, progression-free survival adverse effects other than cardiac damage, quality of life, tumor response and costs, would be of great interest. Specific anthracycline pharmacokinetic studies in children with cancer might help generate knowledge regarding optimal infusion duration (as clearance of anthracycline is different in children as compared to adults).			
PICO 2—infusion duration of anthracycline chemotherapy: 6 hr or more versus 1–6 hr				
Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ■	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐
We recommend against offering this option ☐	We suggest not offering this option ☐	We suggest offering this option ☐	We recommend offering this option ☐	
Recommendation (text)	No recommendation			
Justification	Only one study compared an anthracycline chemotherapy infusion time between 1 and 6 hr (in this case 1 hr) with an infusion time longer than 6 hr (in this case 24 hr). This was a pediatric study. The reported outcomes were clinical heart failure (risk ratio not estimable) and tumor response (no significant differences). It should be noted that the follow-up time was very short, that is, 7 days. Given this extreme scarcity of evidence, the panel reluctantly had to admit that it would not be able to formulate a recommendation for a specific time for anthracycline chemotherapy infusion of 1 hr or longer.			

(Continues)

TABLE 4 (Continued)

PICO 2—infusion duration of anthracycline chemotherapy: 6 hr or more versus 1–6 hr	
Subgroup considerations	None described.
Implementation considerations	As the panel was not able to make a recommendation other than a strong recommendation (based on very low to moderate quality evidence) in favor of an infusion duration of 1 hr or longer, it seems logical for centers who do not do a push (i.e., < 1 hr) infusion to either continue with their current approach or to uniform their approach with other adjacent centers.
Monitoring and evaluation	None described.
Research priorities	The panel felt a large randomized controlled trial is needed to explore optimal infusion times of anthracycline chemotherapy in children with cancer. Randomizing patients among two groups with an infusion duration of 1 hr versus 6 hr, taking into account overall survival, clinical heart failure and subclinical cardiac dysfunction, progression-free survival adverse effects other than cardiac damage, quality of life, tumor response and costs, would be of great interest. Specific anthracycline pharmacokinetic studies in children with cancer might help generate knowledge regarding optimal infusion duration (as clearance of anthracycline is different in children as compared to adults).

TABLE 5 Key recommendations regarding the infusion duration of anthracycline chemotherapy

Recommendation	Type	Strength	Level of evidence
We recommend in favor of an anthracycline infusion duration of at least 1 h in children with cancer.	Clinical	Strong	Very low to moderate
For anthracycline chemotherapy infusion durations of 1 hr or longer, a recommendation for a specific infusion duration is at this moment not possible.	n/a	n/a	Low
We recommend the execution of specific anthracycline pharmacokinetic studies in children with cancer.	Research	n/a	n/a
We recommend a large randomized controlled trial to explore optimal infusion times of anthracycline chemotherapy in children with cancer, taking into account overall survival, clinical heart failure, subclinical cardiac dysfunction, progression free survival, adverse effects other than cardiac damage, quality of life, tumor response, and costs.	Research	n/a	n/a

systematic review themselves, or use an existing synthesis of knowledge. The latter was the case on this topic, as a recently published Cochrane review was used as a starting point for this guideline.[13] This is not only advantageous for the obvious reason of convenience, but we also believe that with the transition of a systematic review to a CPG, the translational gap between research and practice is bridged.

The transition of a systematic review to a CPG is however not a matter of rewriting conclusions to recommendations. There are essential steps that need to be taken before formulating recommendations. First, the search of the systematic review should be updated to guarantee no eligible studies are published after publication of the review. Second, the quality of the evidence should be judged by assessing the body of evidence per outcome (in line with the GRADE methodology), whereas systematic reviews often limit quality appraisal to assessment of bias per study. Third, the evidence including the quality appraisal should be summarized in updated evidence tables, which can be used as a basis for the evidence-to-decision framework. This framework should be completed with a comprehensive, multidisciplinary guideline development group, where it combines the identified evidence with the represented expert knowledge. After these steps, the guideline development group can formulate recommendations.

Currently, anthracyclines are still widely and effectively used in treating children with cancer. A disadvantage of this class of chemotherapy is the potential cardiotoxicity, which is reflected in a 15-fold greater risk of heart failure in childhood cancer survivors as compared to the general population.[1,23] Multiple strategies to reduce this cardiotoxicity have been proposed, in which prolonging the infusion time was one of the first.[6] Unfortunately, as is shown in this report, evidence in children regarding the effects of different infusion durations is still scarcely available. In situations where little evidence is available, it might be worthwhile to explore indirect evidence, as this might be the "next best thing". To this matter, we included four adult studies, in which the highest level of evidence quality was moderate (including the downgrading of one level for indirectness).

In a series regarding the GRADE methodology, the situation of (very) low quality evidence and/or an unknown or close balance between desirable and undesirable effects is addressed.[24] Although

the often occurring reluctance to make a recommendation in this situation is acknowledged, the authors encourage guideline developers to still attempt to formulate recommendations, as in a clinical situation there is often not an option to refrain from making a decision. Although the guideline panel was aware of this statement and fully supported the intention, the panel felt there was unquestionably too little valuable evidence and too much missing information regarding the balance of desirable and undesirable effects to formulate a recommendation regarding an infusion duration of 6 hr or more versus an infusion duration between 1 and 6 hr. The panel did, however, feel that with the available evidence (comparing a ≥1 hr infusion vs. a push infusion), supplemented with the represented expert knowledge in the guideline development panel and the panel notion of the relatively high occurrence and potential severity of clinical heart failure, a recommendation in favor of an anthracycline infusion duration of ≥1 hr was justifiable. Given the large effect on clinical heart failure (critical outcome, moderate quality evidence), this recommendation was categorized as strong.

Regarding limitations of this guideline effort, it should be noted that the inclusion of studies was limited to randomized controlled trials describing cardiotoxicity. Therefore, analyses of other effects (tumor response, progression-free survival, overall survival, adverse effects other than cardiac damage, quality of life) were possibly based on only a subgroup of trials comparing different anthracycline infusion durations.

In short, this guideline effort is a first step in defining an optimal anthracycline infusion duration with respect to cardiotoxicity in children with cancer. We recommend in favor of an anthracycline infusion duration of at least 1 hr (strong recommendation, very low to moderate quality of evidence). We were not able to formulate a recommendation regarding a precise optimal prolonged infusion duration. Research priorities were set for a large, randomized trial exploring optimal infusion times and for specific anthracycline pharmacokinetic studies. This study also serves as a practice example of the essential steps that need to be taken when using a published systematic review to develop a high-quality CPG.

ACKNOWLEDGMENTS

We thank the Dutch pediatric oncology patient and parent association "Vereniging Ouders, Kinderen en Kanker" for playing an active role in the recruitment of parent representatives. The project "Towards evidence-based guidelines for supportive care in childhood oncology" is supported by the Alpe d'HuZes foundation/Dutch Cancer Society (RUG 2013-6345). The editorial base of Cochrane Childhood Cancer is funded by Stichting Kinderen Kankervrij (KiKa). The funding sources had no role in the study design, the preparation of the manuscript, or the decision to submit the manuscript for publication.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ORCID

Erik A.H. Loeffen http://orcid.org/0000-0003-4514-3358

REFERENCES

1. van der Pal HJ, van Dalen EC, van Delden E, et al. High risk of symptomatic cardiac events in childhood cancer survivors. *J Clin Oncol*. 2012;30(13):1429–1437.
2. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009;8(339):b4606.
3. van Dalen EC, van der Pal HJH, Kok WEM, et al. Clinical heart failure in a cohort of children treated with anthracyclines: a long-term follow-up study. *Eur J Cancer*. 2006;42(18):3191–3198.
4. Kremer LCM, van der Pal HJH, Offringa M, et al. Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systematic review. *Ann Oncol*. 2002;13(6):819–829.
5. Brouwer CAJ, Postma A, Vonk JM, et al. Systolic and diastolic dysfunction in long-term adult survivors of childhood cancer. *Eur J Cancer*. 2011;47(16):2453–2462.
6. Legha SS, Benjamin RS, Mackay B, et al. Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. *Ann Intern Med*. 1982;96(2):133–139.
7. Lipshultz SE, Giantris AL, Lipsitz SR, et al. Doxorubicin administration by continuous infusion is not cardioprotective: the Dana-Farber 91-01 Acute Lymphoblastic Leukemia protocol. *J Clin Oncol*. 2002;20(6):1677–1682.
8. Batist BG, Ramakrishnan G, Rao CS, et al. Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and multicenter trial of metastatic breast cancer. *J Clin Oncol*. 2001;19(5):1444–1454.
9. van Dalen EC, Michiels EMC, Caron HN, et al. Different anthracycline derivates for reducing cardiotoxicity in cancer patients. *Cochrane Database Syst Rev*. 2010 Mar 17;(3):CD005006. doi: 10.1002/14651858.CD005006.pub3.
10. van Dalen EC, Raphaël MF, Caron HN, et al. Treatment including anthracyclines versus treatment not including anthracyclines for childhood cancer. *Cochrane Database Syst Rev*. 2014 Sep 4;(9):CD006647. doi: 10.1002/14651858.CD006647.pub4.
11. van Dalen EC, Caron HN, Dickinson HO, et al. Cardioprotective interventions for cancer patients receiving anthracyclines. *Cochrane Database Syst Rev*. 2011 Apr 16;(2):CD003917. doi: 10.1002/14651858.CD003917.pub3.
12. van Dalen EC, van der Pal HJH, Kremer LC. Different dosage schedules for reducing cardiotoxicity in people with cancer receiving anthracycline chemotherapy. *Cochrane Database Syst Rev*. 2016 Mar 3;3:CD005008. doi: 10.1002/14651858.CD005008.pub4.
13. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(April):924–926.
14. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401–406.
15. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383–394.
16. Escherich G, Göbel U, Jorch N, et al. Daunorubicin-induced cell kill with 1-hour versus 24-hour infusions: a randomized comparison in children with newly diagnosed acute lymphoblastic leukemia. *Klin Pädiatrie*. 2007;219(3):134–138.
17. Lipshultz SE, Miller TL, Lipsitz SR, et al. Continuous versus bolus infusion of doxorubicin in children with ALL: long-term cardiac outcomes. *Pediatrics*. 2012;130(6):1003–1011.

18. Steinherz PG, Redner A, Steinherz L, et al. Development of a new intensive therapy for acute lymphoblastic leukemia in children at increased risk of early relapse. The Memorial Sloan-Kettering-New\sYork-II protocol. *Cancer*. 1993;72(10):3120–3130.
19. Zalupski M, Metch B, Balcerzak S, et al. Phase III comparison of doxorubicin and dacarbazine given by bolus versus infusion in patients with soft-tissue sarcomas: a Southwest Oncology Group study. *J Natl Cancer Inst*. 1991;83(13):926–932.
20. Hortobagyi GN, Yap HY, Kau SW, et al. A comparative study of doxorubicin and epirubicin in patients with metastatic breast cancer. *Am J Clin Oncol*. 1989;12(1):57–62.
21. Casper ES, Gaynor JJ, Hajdu SI, et al. A prospective randomized trial of adjuvant chemotherapy with bolus versus continuous infusion of doxorubicin in patients with high-grade extremity soft tissue sarcoma and an analysis of prognostic factors. *Cancer* 1991;68(6):1221–1229.
22. Shapira J, Gotfried M, Lishner M, et al. Reduced cardiotoxicity of doxorubicin by a 6-hour infusion regimen. A prospective randomized evaluation. *Cancer* 1990;65(4):870–873.
23. Armenian SH, Kremer LC, Sklar C. Approaches to reduce the long-term burden of treatment-related complications in survivors of childhood cancer. *Am Soc Clin Oncol Educ Book*. 2015;196–204.
24. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol*. 2013;66(7):719–725.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Loeffen EAH, van Dalen EC, Mulder RL, et al. The duration of anthracycline infusion should be at least one hour in children with cancer, a clinical practice guideline. *Pediatr Blood Cancer*. 2018;65:e26867. https://doi.org/10.1002/pbc.26867