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Critical appraisal of clinical guidelines for prevention and management of doxorubicin-induced cardiotoxicity

Iman Moustafa[1,2,3], Michelle Viljoen[4], Velisha Ann Perumal-Pillay[1] and Frasia Oosthuizen[1]

Abstract

Objective: Doxorubicin is a valuable chemotherapeutic drug; however, it is associated with a high risk of cardiotoxicity. Several institutions and organizations have developed guidelines for risk factor assessment, monitoring and prevention strategies against chemotherapy-induced cardiotoxicity. This review aimed to assess the quality of current practice guidelines, using the Appraisal of Guidelines for Research and Evaluation II (AGREE II). This tool was used to compare the recommendations with regards to their strength and evidence recommendations were based on.

Data Sources: This review identified guidelines in literature from January 1960 to February 6, 2022, through a systematic search that included PubMed, EMBASE, MEDLINE, Cochrane Database and Google Scholar. The quality, consistency and the strength of supporting evidence was evaluated using the AGREE II method.

Data Summary: Eight guidelines met the inclusion criteria and 144 recommendations were extracted from these guidelines. The results from the AGREE II evaluation showed that the total assessment scores of guidelines ranged from 2 to 5, indicating the guidelines need modifications. The recommendations were evaluated according to the references used, and it was found that 12 (11%) recommendations had high evidence, 36 (33%) had moderate evidence, 38 (35.19%) had low and 22 (20.37%) had insufficient evidence. Recommendations for risk factors assessment, prophylaxis of cardiotoxicity, management of cardiotoxicity and monitoring of cardiotoxicity were quite varied amongst the different guidelines evaluated.

Conclusions: All studied guidelines need modifications as per the AGREE II evaluating tool. Several shortcomings were identified, including a lack of evidence-based studies supporting the recommendations in the guidelines.

Keywords

Doxorubicin, assessment, monitoring, management, guideline

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Background

Doxorubicin is a member of the anthracycline group of chemotherapeutic drugs which are highly effective for the treatment of solid tumours and haematological malignancies.[1] Doxorubicin is however associated with a high risk of cardiotoxicity.[2] The risk factors for doxorubicin-induced cardiotoxicity include the cumulative dose received, female gender, age (more than 65 and less than 18 years old), renal failure, previous radiation therapy involving the heart, some concomitant chemotherapy such as alkylating agents (carboplatin, cisplatin and cyclophosphamide); taxanes (docetaxel, paclitaxel and cabazitaxel); topoisomerase inhibitors (etoposide, vincristine and vinblastine); antimetabolites (cytarabine and 5-flurouracil); or immuno-and targeted therapies (trastuzumab), pre-existing cardiac diseases, arterial hypertension and genetic factors. Other risk factors that may increase doxorubicin cardiotoxicity include systolic dysfunction, vascular disease, hypertension, stroke, transient ischemic attack, diabetes mellitus,

[1]Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa
[2]Pharmaceutical care department, King Abdulaziz Hospital, Ministry of the National Guard - Health Affairs, AlHasa, Saudi Arabia
[3]King Abdullah International Medical Research Center, AlHasa, Saudi Arabia
[4]School of Pharmacy, University of the Western Cape, Bellville, South Africa

Corresponding author:
Iman Moustafa, King Abdulaziz Medical City, AlHasa, Saudi Arabia.
Email: emooo74@yahoo.com

renal failure or metabolic disorders in addition to lifestyle factors such as smoking, being overweight, or being physically inactive. Oncologists and cardiologists mainly depend on experience to recognize high-risk patients and manage cardiotoxicity due to a lack of evidence-based information for the assessment of potential risks and management of cardiotoxic chemotherapy.[3–5]

Monitoring and prevention strategies against doxorubicin-induced cardiotoxicity are varied.[3,6–12] Several institutions and organizations, including the American Society of Clinical Oncology (ASCO), New South Wales guidelines (NSW), International Society of Geriatric Oncology (SIOG), Spanish Society of Medical Oncology (SEOM), European Society of Cardiology (ESC), European Society of Medical Oncology (ESMO), National Cancer Institute (NCI) and Canadian Cardiovascular Society (CCS) have developed guidelines for risk factor assessment, monitoring and prevention strategies against chemotherapy-induced cardiotoxicity.[3,6–12] However, the consistency of these recommendations and the supporting evidence have not been evaluated previously.

Aim of the review

This review aimed to assess the quality of clinical guidelines for prevention and management of doxorubicin-induced cardiotoxicity, using the Appraisal of Guidelines for Research and Evaluation II (AGREE II), a widely used guideline evaluation tool.[13] In addition to comparing the recommendations, supporting evidence for these guidelines was also evaluated.

Methods

Data sources and search strategy

Websites of oncology and cardiology organizations, in addition to electronic databases, including PubMed, EMBASE, MEDLINE, Cochrane Database and Google Scholar, were searched. Reference lists of guidelines were also checked for any other relevant papers. The search included publications from January 1960 to February 6, 2022. The medical subject headings (MeSH) used were 'guideline', 'doxorubicin', 'anthracycline', 'prophylaxis', 'management' and 'cardiotoxicity'.[3,6–12]

Eligibility criteria

Guidelines developed for risk assessment, prophylaxis, and management and monitoring of anthracycline-induced cardiotoxicity were searched. Only guidelines written in English were included for the review and the most current update of the guidelines was used. Guidelines not covering anthracyclines with a focus on chemotherapy induced cardiotoxicity were excluded.

Data extraction

Characteristics of included guidelines and comparison of the strength of supporting evidence. Information extracted from the guidelines included a description of the guideline including publication year, country of origin, dates of references used, the developing institution or organization and number of recommendations included in the guidelines, as well as the name of grading system used by the developers in the guidelines to evaluate the strength and evidence based on the recommendations (Table 1).

Comparison of recommendations. The recommendations included in the guidelines were compared and analyzed. Data pertaining to recommendations was extracted and categorized into four main categories; risk factors assessment (15 items), prophylaxis of cardiotoxicity (17 items), management of cardiotoxicity (16 items) and monitoring of cardiotoxicity (9 items). Recommendations were rated YES or NO as per inclusion in the specific guideline (Table 2).

Assessment of the quality of practice clinical guidelines (AGREE II evaluation). AGREE II is a subjective tool used to evaluate the quality of guidelines. AGREE II consists of six quality domains with 23 item tools; the domains are evaluated and a score given as a percentage. Items are evaluated using a Likert scale.

Domain 1 (items 1–3) reviews the overall aim of the guideline, the precise health questions, and the target population. Domain 2 (items 4–6) reviews stakeholder involvement, the guideline development process, and the views of target users. Domain 3 (items 7–14) reviews the rigour of the development process used for gathering and synthesizing evidence and formulating the recommendations. Domain 4 (items 15–17) reviews the clarity of presentation including language, structure and format of the guideline. Domain 5 (items 18–21) reviews applicability, barriers to implementation, strategies to improve uptake and resource implications of application. Domain 6 (items 22–23) reviews editorial independence of the funding body and the conflicts of interest of guideline development members.

Before applying the AGREE II evaluation criteria to the guidelines, the guideline documents were carefully reviewed. All information regarding the guideline evaluation process was identified and summarized in a separate sheet (Table 3). One appraiser scored the guidelines.

Calculating AGREE II items. Each of the 23 AGREE II items was rated on a 7-point Likert scale (1–strongly disagree, 7–strongly agree), and a score between 2 and 6 was assigned when the reporting item did not meet the full criteria.[14] A score is assigned depending on the

Table 1. Characteristics of included guidelines.

			Recommendation		Recommendations Strength								Recommendation Evidence-based											
					Risk assessment			Monitoring			Management			Risk assessment			Monitoring			Management				
Guideline	Country	Search period	N	Grading	S	M	L	S	M	L	S	M	L	H	M	L	I	H	M	L	I	H	M	L	I
ASCO 2017	USA	1996–2016	17	GLIDES	0	2	0	7	8	0	3	2	0	0	1	1	0	1	10	1	6	0	2	0	3
CCS 2016	Canada	ND	12	GRADE	1	0	3	1	0	4	1	0	2	0	1	3	0	1	4	0	0	1	1	1	0
ESMO 2020	150 countries, Switzerland	1975 -2018	40	IDSA	1	0	0	8	1	2	4	3	4	1	0	0	0	5	0	6	0	2	3	4	2
NCCN 2021	USA (NCI)	ND	12	NCCN	0	0	5	0	0	4	0	0	3	0	0	5	0	0	0	4	0	0	0	3	0
SEOM 2018	Spain	ND	20	IDSA	3	0	0	3	3	1	4	0	0	0	0	0	3	1	1	10	0	0	1	0	3
SIOG 2011	Switzerland	ND	19	OCEBMS	4	0	0	3	0	0	10	0	0	0	4	0	0	0	2	0	1	0	6	0	4
Total			120		9	2	8	22	12	11	22	5	9	1	6	9	3	8	17	21	7	3	13	8	12

American Society of Clinical Oncology (ASCO),[6] CCS Canadian Cardiovascular Society,[12] ESC: European society of cardiology,[3] ESMO: European society of medical oncology,[10] NCI: National Cancer Institute, NCCN: National comprehensive cancer network,[11] NSW: New South Wales guideline,[7] ND: Not determined, SEOM: Spanish Society of Medical Oncology,[9] SIOG: International Society of Geriatric Oncology,[8] GLIDES: Guidelines Into Decision Support methodology, GRADE: Grading of Recommendations Assessment, Development, and Evaluation system, IDSA: Infectious Diseases Society of America-United States Public Health Service Grading System. NCCN Categories of Evidence and Consensus. OCEBMS: Oxford Centre for Evidence-based Medicine, N: number S: strong, M: moderate, L: low, H: high, I: insufficient.

completeness and quality of reporting. Scores increase as more criteria are met and considerations addressed.[14]

A score of 1 (Strongly Disagree) was assigned when there was no information that is relevant to the AGREE II item, if the concept was very poorly reported, or if the authors stated explicitly that criteria were not met. Score of 7 (Strongly Agree) was assigned if the quality of reporting was exceptional and where the full criteria was met. Scores between 2 and 6 was assigned when the reporting of the AGREE II item did not meet the full criteria or some items were missing or poorly reported. The overall assessment included the rating of the quality of the guideline and whether the guideline would be recommended for use in practice or not (Table 3).

Calculating AGREE II domains. Every domain percentage (%) was calculated according to the following equation:

$$\begin{aligned}\text{Maximum possible score} &= 7(\text{strongly agree}) \\ &\times (\text{number of domain items}) \\ &\times 1(\text{appraiser numbers})\end{aligned}$$

$$\text{Obtained score} = \text{the sum of total items scores}$$

$$\begin{aligned}\text{The domain score}(\%) &= \textit{Obtained score} \\ &- \textit{Minimum possible score} \\ &/ \textit{Maximum possible score} \\ &- \textit{Minimum possible score}\end{aligned}$$

All domains scores were totaled to get overall average score for each guidelines; the higher the average score, the stronger the guidelines.

Assessment of the guidelines by Likert scale. Guidelines were assessed via scoring from 1 to 7 on a Likert scale; score of 1 (lowest possible quality), Score 2–6 (indicated the need for modification) and score of 7 (highest possible quality).

As the domains scores were calculated in percentages as explained above, the percentages were transformed to a Likert scale.

Hundred percent was considered as 100 points and the equivalent of 7 on a Likert scale and calculated as 100/7 = 14.29.

A score of 1 is calculated as (14.29 × 1 = 14.29%), score 2 is (14.29 × 2 = 28.57%), score 3 is (14.29 x3 = 42.87%), score 4 is (14.29 × 4 = 57.16), score 5 is (14.29 × 5 = 71.45), score 6 is (14.29 × 6 = 85.74) and score 7 is (14.29 × 7 = 100.03).

Results

Search results

The search strategy, as depicted in Figure 1, identified a total of 63 331 articles. After the exclusion of articles not

Table 2. Comparison of guidelines.

	ASCO	CCS	ESC	ESMO	NCCN	NSW	SEMO	SIOG
1) Risk factor assessment								
Age	Y ≥ 60 y	Y > 50 y	Y < 18, > 65 y	Y < 10, > 75 y	Y > 65 y	Y < 15, > 65 y	Y < 15, > 65 y	Y(ND)
Gender	N	Y(F)	Y(F)	N	N	Y(F)	Y(F)	Y(M)
Ethnicity	African American	non-Caucasian	African	N	N	N	N	N
Cumulative dose(mg/m^2)	Y (>250)	Y(ND)	Y(400)	Y (>300)	Y (>250)	Y (>250)	Y (>240)	Y(ND)
Previous radiotherapy(unit used: gray)	Y(>30)	Y(ND)	Y(ND)	Y(ND)	Y(ND)	Y (>30)	Y(>30)	Y(ND)
Comorbidities	Y	Y	Y	Y	Y	Y	Y	Y
Cardiac disease	Y	Y	Y	Y	Y	Y	Y	Y
Concomitant chemotherapy	Y	N	Y	Y	N	Y	Y	Y
Previous chemotherapy	N	Y	N	N	N	Y	N	N
Smoking	Y	Y	Y	Y	Y	Y	Y	Y
Physically inactive	N	N	N	N	N	Y	Y	Y
Obesity	Y	N	Y	Y	Y	Y	Y	Y
Genetic factor	N	N	Y	N	N	N	N	N
High alcohol intake	N	N	Y	N	Y	N	N	N
Bolus anthracycline administration	N	N	N	N	N	Y	N	N
Number of items included	9	9	12	8	8	12	10	10
2) Prophylaxis of cardiotoxicity								
History and physical examination	Y	Y	Y	Y	Y	Y	Y	Y
Avoid anthracycline if alternative	Y	N	N	Y	N	Y	Y	N
Manage cardiovascular risk factors[#]	Y	Y	Y	Y	Y	Y	Y	Y
Total cumulative dose limited (mg/m^2)	N	N	Y (<360)	N	N	Y(450–500)	N	Y (450)
Low or modified RT	Y	Y	N	N	N	N	N	N
Continuous infusion	Y	N	Y	N	N	Y	N	Y
Liposomal doxorubicin	Y	N	Y	N	N	Y	N	Y
Dexrazoxane*	Y	N	Y	Y	N	Y	N	Y
Use of beta-blockers or ACE inhibitors, ARBs	N	Y	Y	Y	Y	Y	Y	N
Patient education	N	Y	Y	Y	Y	Y	Y	Y
Anticoagulant (enoxaparin, rivaroxaban /apixaban	N	N	N	Y	N	N	Y	N
Antiplatelet (aspirin)	N	N	N	Y	N	N	N	N
Diuretic (spironolactone)	N	N	N	Y	N	N	N	N
Combination of ACE-I/BB (enalapril, carvedilol	N	N	N	Y	N	N	N	N
Healthy lifestyle[##]	Y	Y	Y	Y	Y	Y	N	Y
Statins	N	Y	Y	Y	N	N	Y	N
Avoid taxol and trastuzumab concurrent	N	N	N	N	N	N	N	Y
Number of items included	8	7	10	12	5	10	7	9
3) Management of cardiotoxicity (cardiomyopathy – heart failure)								
Complete history and physical examination	Y	Y	Y	Y	Y	Y	Y	Y
Routine clinic assessment[$]	Y	Y	N	Y	N	N	Y	N

(continued)

Table 2. Continued.

	ASCO	CCS	ESC	ESMO	NCCN	NSW	SEMO	SIOG
Determine the stage of cardiomyopathy	N	N	Y	Y	Y	N	N	N
Referral to cardiologist or cardio-oncologist	Y	Y	Y	Y	Y	Y	Y	Y
Manage cardiovascular risk factors[#]	N	Y	Y	Y	Y	Y	Y	Y
Use of beta-blockers or ACE inhibitors, ARBs	N	Y	N	Y	N	Y	Y	N
Antiplatelet (aspirin)	N	N	N	Y	N	N	N	N
Diuretic (spironolactone)	N	Y	N	Y	N	N	N	N
Combination of ACE-I/BB	N	N	N	Y	N	N	N	N
Patient education	N	Y	Y	Y	N	Y	Y	Y
Anticoagulant	N	Y	N	Y	N	N	Y	N
Healthy lifestyle[##]	N	Y	Y	Y	Y	Y	N	Y
Statins	N	Y	N	Y	N	N	N	N
Alternate antineoplastic treatments	N	Y	N	N	N	N	N	N
Corticosteroid	N	N	N	Y	N	N	N	N
Discontinuation decision	N[$$]	N	N	Y[$$]	N	Y	N	N
Number of items included	3	11	6	15	5	7	7	5
4) Monitoring of cardiotoxicity								
Electrocardiogram	Y	N	N	Y	N	Y	Y	N
Echocardiogram	Y	Y	Y	Y	Y	Y	Y	Y
Cardiac magnetic resonance imaging (MRI)	Y	Y	Y	Y	N	N	N	N
Multigated acquisition (MUGA)	Y	Y	Y	Y	N	Y	N	Y
Global longitudinal strain (GLS)	N	N	Y	Y	N	N	Y	N
Cardiac biomarkers	Y	Y	Y	Y	Y	N	Y	N
Echocardiography-derived strain imaging	Y	Y	N	N	N	N	N	N
Endomyocardial biopsy	N	N	N	Y	N	N	N	N
Surveillance (month)	Y(6 -12)	N	Y(3)	Y(6-12)	Y(6–12)	Y(NA)	Y(NA)	Y(NA)
Number of items included	7	5	6	8	3	4	5	3
Total number of items included	27	32	34	43	21	33	29	27

ASCO: American Society of Clinical Oncology; ACE: angiotensin-converting-enzyme inhibitors; ARBs: angiotensin II receptor blockers; CCS: Canadian Cardiovascular Society; Comorbidities: hypertension, diabetic, hyperlipidemia. Concomitant chemotherapy: as trastuzumab, alkylating or antimicrotubular agents, immuno- and targeted therapies; ESC: European Society of Cardiology; ESMO: European Society of Medical Oncology; SEOM: Spanish Society of Medical Oncology; SIOG: International Society of Geriatric Oncology; NCCN: National Comprehensive Cancer Network; NSW: New South Wales guideline; N: no; ND: not determine; Y: yes; y: year.

*With high-dose anthracyclines (e.g., doxorubicin $\geq$ 250 mg/m^2, epirubicin $\geq$ 600 mg/m^2).

[#]Hypertension, lipids, smoking, obesity, metabolic syndrome, diabetes.

[##]Regular physical activity, healthy diet.

[$]Monitoring work-up.

[$$]Refer to oncologist.

Table 3. Checklist for AGREE II items and mean scores in each domain.

Domain	Item*	ASCO	CCS	ESC	ESMO	NCCN	NSW	SEOM	SIOG
Domain 1 Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.	6	6	2	6	6	3	2	1
	2. The health question(s) covered by the guideline is (are) specifically described.	6	6	2	6	6	3	2	1
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	5	5	2	6	6	4	2	3
	Domain 1 score (%), mean = 49.22 #	77.78	77.78	16.67	83.33	83.33	38.89	16.67	27.78
Domain 2 Stakeholder involvement	4. The guideline development group includes individuals from all relevant professional groups.	7	5	2	5	7	1	2	1
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	5	5	2	5	6	3	3	2
	6. The target users of the guideline are clearly defined.	4	4	2	4	5	4	3	2
	Domain 2 score (%), mean = 47.23#	72.22	61.11	16.67	61.11	83.33	27.78	27.78	27.78
Domain 3 Rigour of development	7. Systematic methods were used to search for evidence.	6	3	2	6	3	3	3	2
	8. The criteria for selecting the evidence are clearly described.	5	2	2	5	3	4	3	2
	9. The strengths and limitations of the body of evidence are clearly described.	4	3	2	4	3	3	3	2
	10. The methods for formulating the recommendations are clearly described.	5	6	2	5	7	7	6	3
	11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	4	3	2	4	4	7	3	2
	12. There is an explicit link between the recommendations and the supporting evidence.	4	4	2	4	4	7	3	3
	13. The guideline has been externally reviewed by experts prior to its publication.	6	6	2	6	7	3	3	2
	14. A procedure for updating the guideline is provided.	3	2	1	2	7	7	3	1
	Domain 3 score (%), mean = 45.38 #	60.42	43.75	14.58	58.33	62.5	68.75	39.58	18.75
Domain 4 Clarity of presentation	15. The recommendations are specific and unambiguous.	5	6	3	6	7	7	6	4
	16. The different options for management of the condition or health issue are clearly presented.	4	5	2	5	7	7	5	3
	17. Key recommendations are easily identifiable.	5	6	2	6	7	7	7	4
	Domain 4 score (%), mean = 68.75#	61.11	77.78	22.22	77.78	100	100	83.33	27.78
Domain 5 Applicability	18. The guideline describes facilitators and barriers to its application.	2	3	2	3	2	3	3	2
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	6	6	3	6	7	7	5	4
	20. The potential resource implications of applying the recommendations have been considered.	4	4	2	4	4	4	3	3
	21. The guideline presents monitoring and/or auditing criteria.	6	6	2	5	6	7	5	3
	Domain 5 score (%), mean = 54.17#	58.33	62.5	20.83	58.33	62.5	70.83	66.67	33.33

(continued)

Table 3. Continued.

Domain	Item*	ASCO	CCS	ESC	ESMO	NCCN	NSW	SEOM	SIOG
Domain 6 Editorial independence	22. The views of the funding body have not influenced the content of the guideline.	6	6	6	7	3	2	2	7
	23. Competing interests of guideline development group members have been recorded and addressed.	7	1	1	1	1	2	7	7
	Domain 6 score (%), mean = 52.08	91.66	41.67	41.67	50	16.67	16.67	58.33	100
	Average domains of guideline, Overall guideline assessment (%)	70.25	57.36	22.11	64.81	68.01	53.82	48.73	39.24
	Overall guideline assessment (Likert scale) [##]	5	4	2	4	5	4	3	2

ASCO: American Society of Clinical Oncology; CCS: Canadian Cardiovascular Society; ESC: European Society of Cardiology; ESMO: European Society of Medical Oncology; NCI: National Cancer Institute; NCCN: National comprehensive cancer network; NSW: New South Wales guideline; SEOM: Spanish Society of Medical Oncology; SIOG: International Society of Geriatric Oncology.[3,6–12]

*Item score: from 1 to 7.

Score of 1 (Strongly Disagree), when no information relevant to AGREE II item, if the concept is very poorly reported, or if the authors state explicitly that criteria were not met.

Scores between 2 and 6: assigned when the reporting of the AGREE II item does not meet the full criteria or considerations.[14]

Score of 7 (Strongly Agree), if the quality of reporting is exceptional and where the full criteria and considerations articulated in the user's manual have been met.

[#]Domain calculation:

Maximum possible score = 7 (strongly agree) x (domain items) x 1 (appraiser).

Minimum possible score = 1 (strongly disagree) x (domain items) x 1 (appraiser).

Obtained score = the sum of total items scores.

The domain score(%) = *Obtained score − Minimum possible score / Maximum possible score − Minimum possible score*Average total score: highest percentage more strongly.

[##]Transform percentage % of domain score to Likert scale.

Percentage is 100 points.

Likert scale is 7 scores (1 2 3 4 5 6 7).

Every part of Likert scale = 100/7.

The highest is 7 and the lowest is 1.

The estimation of numerical value of specific score 100/7 so every score 14.29.

A score of 1 will have 1 part 14.29%, Score 2 have 2 parts will 28.57%, score 3 is 42.87%, score 4 is 57.16, score 5 is 71.45.

The overall guideline assessment, considered all appraisal items considered score from 1 to 7.

Score of 1 (lowest possible quality).

Score 2–6 (The guideline needs modification).

Score of 7 (Highest possible quality).

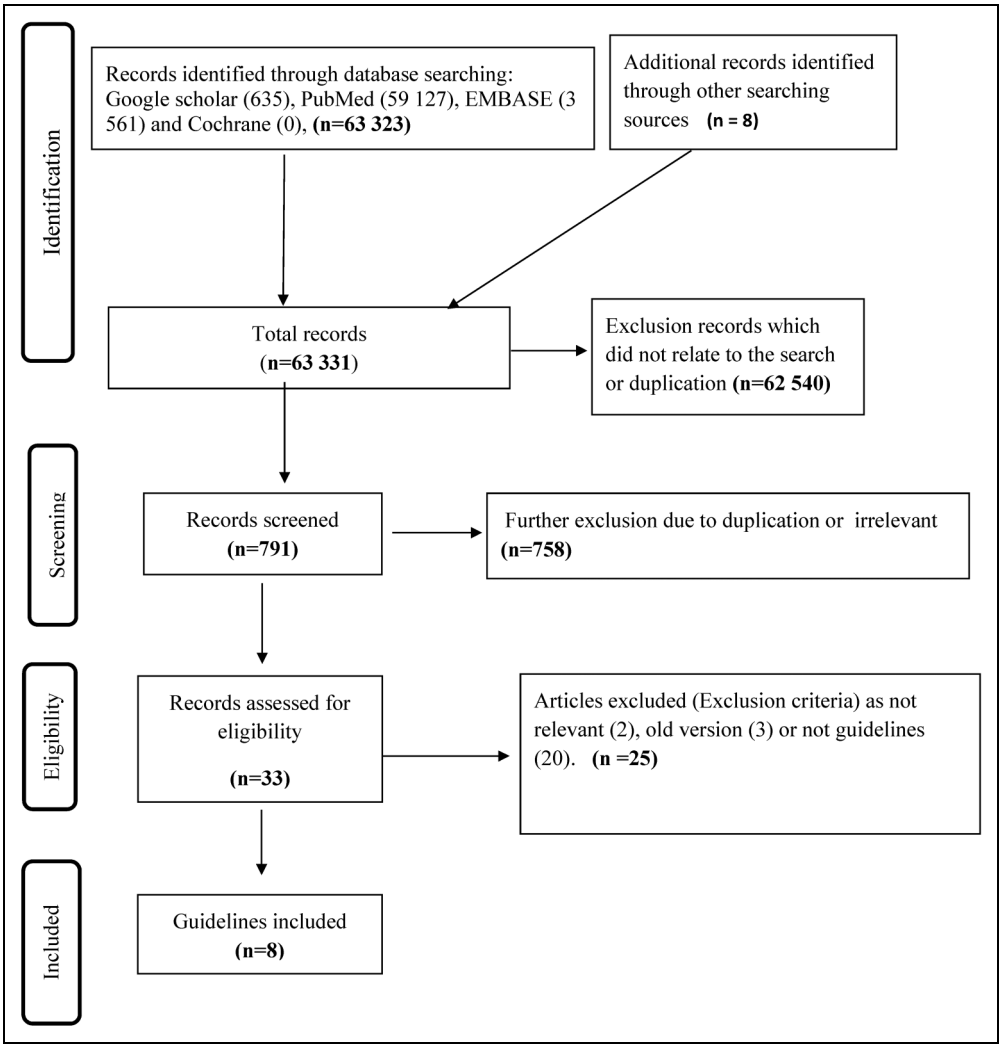

Figure 1. Flow chart demonstrating the guidelines selection.

related to the topic, 791 remained. A further 758 articles were excluded due to duplication and lack of relevance as some guidelines did not focus on cardiotoxicity and others did not focus on chemotherapy-induced cardiotoxicity; an additional 25 articles did not meet the eligibility criteria as they were not relevant (2 articles), older version (3 articles) or not guidelines (20 articles). The final number of articles selected was eight (0.013% of the initial search result) (Figure 1).

Evaluating the recommendations included in the guidelines. The eight guidelines had 144 recommendations in total; 120 recommendations were evaluated according to grading system however 24 did not have any grading system.[3,6–12] All guidelines, except ESC and NSW, have their owned grading system. However, the guidelines used different grading systems. The grading systems evaluated the strength of recommendations (100 recommendations) in addition to evidence used (108 recommendations). For instance, ASCO guidelines were evaluated using Guidelines into Decision Support methodology (GLIDES) with 17 recommendations (14.2%); CCS guidelines were evaluated using Grading of Recommendations Assessment (GRADE) that evaluated 12 recommendations (10%); ESMO (40 recommendations; 33.3%) and SEOM (20 recommendations; 16.67%) guidelines used Infectious Diseases Society of America Grading System (IDSA) to evaluate the guidelines recommendations; SIOG was evaluated using the Oxford Centre for Evidence-based Medicine system (19 recommendations; 15.8%), while NCCN guidelines used NCCN evaluating system (12 recommendations; 10%). NSW and ESC did not provide recommendations as clear points; their guidance was supported by consensus panels and some studies (Table 1).

A total of 100 recommendations were included in the listed guidelines and graded according to their own grading systems as strong, moderate or low; 53 recommendations were graded as strong, 19 were graded as moderate and 28 recommendations as low (Table 1).

When recommendations (108) were evaluated according to their evidence-based references, it was found that 12 (11%) recommendations had strong evidence, 36 (33%) had moderate evidence, 38 (35.19%) had low and 22 (20.37%) had insufficient evidence (Table 1).

Comparison of guidelines' recommendations. Table 2 compared 57 items from four main categories. The total number of items included in the guidelines were ASCO (27; 47.37%), CCS (32; 56.14%), ESC (34; 59.65%), ESMO (43; 75.44%), NCCN (21; 36.84%), NSW (33; 57.89%), SEMO (29; 50.88%) and SIOG (27; 47.37%).

Risk assessment category included 15 items that distributed as: ASCO (9 items), CCS (9), ESC (12), ESMO (8), NCCN (8), NSW (12), SEMO (10) and SIOG (10). All guidelines shared five risk items cumulative dose, previous radiotherapy, comorbidities, cardiac disease and smoking; however, the other risk 10 items differed amongst guidelines.

The category on prophylaxis of cardiotoxicity included 17 items as follows: ASCO (8 items), CCS (7), ESC (10), ESMO (12), NCCN (5), NSW (10), SEMO (7) and SIOG (9). Two items were shared amongst guidelines – the history and physical examination item and the management of cardiovascular risk factors.

Management of cardiotoxicity (16 items) were ASCO (3 items), CCS (11), ESC (6), ESMO (15), NCCN (5), NSW (7), SEMO (7) and SIOG (5). Complete history and physical examination item and referral to cardiologist were mentioned in all guidelines nevertheless the other 14 items were different amongst guidelines.

Monitoring of cardiotoxicity included 9 items as follows: ASCO (7 items), CCS (5), ESC (6), ESMO (8), NCCN (3), NSW (4), SEMO (5) and SIOG (3). Echocardiogram was the only item listed in all guidelines. In total, 47 (82.46%) recommendations were discordant between guidelines and 10 recommendations were similar in the guidelines.

Assessment of the quality of practice clinical guidelines (AGREE II evaluation). The overall assessment scores for guidelines evaluations ranged from 2–5; no guideline achieved seven (highest) or one (lowest) for quality. The highest quality guidelines were ASCO and NCCN with both scoring five, and the lowest quality was ESC and SIOG with a score of two. According to the AGREE II evaluating tool, all guidelines needed modifications (Table 3).

The domain scores varied from 16.67% to 100% with an average of 52.96%. The domain with the highest mean score (68.75%) was domain four, clarity of presentation. The lowest score (45.38%) was in domain three, rigour of development. This domain needed improvement in terms of gathering and synthesizing evidence, methods to formulate the recommendations, and to update these. Domain 1, scope and purpose, scored 49.22% and was found to need improvement with regards to the clarification of the overall aim of the guideline, the specific health questions, and the target population. Domain 2, stakeholder involvement, scored 47.23% and needed to focus more on the extent to which the guideline was developed by the appropriate stakeholders and the views of its intended users. Domain 5, applicability, scored 54.17% and needed to facilitate the implementation strategies and resource implications of applying the guideline. Domain 6, editorial independence, scored 52.08% and needed to develop the formulation of recommendations without bias.

Discussion

In this paper, eight guidelines on prevention and management of doxorubicin-induced cardiotoxicity were critically appraisal. As per the AGREE II evaluation, it was concluded that all guidelines needed modifications based on the scores (2–5) in the overall assessment (Table 3). Upon analysis, the recommendations included in the guidelines were unsatisfactory as the evidence-based knowledge was limited (Table 1). There are inconsistencies amongst the various guidelines and inconsistencies amongst the four categories of differentiation (risk factors assessment, prophylaxis of cardiotoxicity, management of cardiotoxicity and monitoring of cardiotoxicity) (Table 2).

The guidelines rate several risk factors for the development of anthracycline-induced cardiotoxicity differently. Four guidelines ESC, NSW, CCS and SEMO considered female gender as high risk while SIOG has an opposing view considering male gender the higher risk. [3,7,10,12] The other guidelines, NCCN, ESMO and ASCO did not mention gender as a risk factor.[3,6–12] Other risk factors included concomitant chemotherapy such as alkylating agents, antimicrotubular agents or immuno- and targeted therapies, were considered risk factors in ESC, while ASCO, SEOM, SIOG and ESMO mentioned trastuzumab only NSW mentioned that any other potentially cardiotoxic drugs such as trastuzumab, paclitaxel, streptozocin, cyclosporin, dacarbazine, dactinomycin, etoposide, cyclophosphamide, ifosfamide, mitomycin, melphalan, vincristine and bleomycin may increase the risk of cardiotoxicity.[6–10] All guidelines considered age as a risk factor, but there were discrepancies with regards to the age at highest risk; ESMO indicates a range of younger than 10 years and older than 75 years, while ESC indicates a range of younger than 18 years and older than 65 years as high risk, NCCN only mentioned age above 65 years, SEOM mentions age younger than 15 years and older than 65 years, and ASCO mentions only older than 60 years. Other risk factors, such as using bolus doxorubicin, were considered only in the NSW guidelines.[7]

The guidelines agreed on the diagnostic procedures and monitoring of cardiotoxicity. Echocardiogram is the preferred initial method of diagnosis and monitoring of cardiotoxicity as

per all guidelines. The cardiac imaging strategy corresponds mainly to the use of transthoracic echocardiogram (TTE) to quantify the LVEF.[15] TTE is the preferred method of measuring cardiac function because of the ability to assess both systolic and diastolic dysfunction. A multigated acquisition (MUGA) scan may be used as an alternative to echocardiogram.[16] All guidelines, except SEMO, agreed on the use of MUGA as an alternative method of monitoring; SEMO did not mention MUGA. Cardiac MRI provides better diagnostic precision and reproducibility than echocardiography and has to be applied in cancer patients with poor echocardiographic images and when the LVEF had borderline values, defined as a decline in LVEF of at least 5% below the base or recorded as 41% to 49%.[18, 3 17] ASCO, CCS, ESC and ESMO recommend this approach while NCCN, NSW, SEMO and SIOG did not mention MRI as an alternative method to TTE.

The biomarker assay techniques are easier to use than cardiac imaging for the detection and monitoring of cardiotoxicity.[19] Many biomarkers such as troponin I, creatine kinase MB, brain natriuretic peptide (BNP) and pro-BNP have been used. Troponin I is the biomarker used the most.[19] Some studies confirmed that the early increased troponin I levels reflect subclinical cardiotoxicity and predict a consequent reduction in the LVEF and, possibly, even heart failure in patients treated with doxorubicin.[20,21] There is no consistency between guidelines for standard monitoring of cardiotoxicity using biomarker assays (Table 2). NCCN, CCS and ESC indicated a lack of high-quality data on the benefits of screening and monitoring by biomarkers nevertheless, they recommended considering biomarker assays in high-risk patients.[3,11] NSW and SIOG did not recommend biomarkers for monitoring. ASCO suggests performing baseline assessments of biomarkers (troponin I and BNP) and periodic measurements during therapy (every cycle) to potentially identify patients who require further cardiac assessment or who are at risk for cardiotoxicity, despite limited data on the effectiveness of this strategy. All guidelines agree to refer the patient to a cardiologist if needed.

There is no agreement amongst these guidelines for one formal method for prevention of cardiotoxicity (Table 2). Not all guidelines support the strategy of replacing doxorubicin bolus administration with a slow continuous doxorubicin infusion over 24–96 h, as slow doxorubicin infusion does not always prevent the risk of cardiotoxicity.[22] The disadvantages of this strategy are prolonged hospitalization, acquired hospital infections and additional costs.[22,23] This strategy further has the possibility of increasing the risk of secondary haematologic malignancy due to increasing the accumulation of DNA-oxidized bases in the peripheral blood mononuclear cells and DNA damage that occur in haematopoietic precursors.[24]

A safe and easy strategy to prevent doxorubicin cardiotoxicity in daily clinical practice is to lower the total cumulative doxorubicin dose below the threshold of 550 mg/m^2.[25] This strategy is supported by ESC (less than 360 mg/m^2), NSW (450–500 mg/m^2) and SIOG (450 mg/m^2) but is not mentioned in the other guidelines (Table 2). The doxorubicin analogue with a high cumulative dose value, such as epirubicin, can be used as replacement, but this is subject to the available cancer protocols and prior anthracycline administration.[26–29] The equivalent factor for dosing doxorubicin and epirubicin is 1:1.6 (440 mg/m^2 and 720 mg/m^2).[26]

Avoiding or minimizing anthracycline use, if an alternative is available and it does not compromise treatment outcomes, is recommended in guidelines.[27] If another alternative non-anthracycline regimen with the same effectiveness or superior is available, it should be considered in patients with high cardiovascular risk as in some cases replacing etoposide instead of doxorubicin in some regimens.[27] This strategy is an approach supported by ASCO, ESC, NSW and ESMO guidelines. ASCO recommended, without evidence, that it is to be based on benefits outweighing harms. ESMO recommended this strategy for a patient who has LVEF <40% citing low evidence studies (retrospective cohort studies or case-control studies). NSW recommended this strategy taking into consideration multidisciplinary decisions and weighing the risks and benefits of the current treatments as well as alternative regimens in the absence of evidence.[7]

Another recommendation is to avoid concurrent administration of anthracycline with taxanes and trastuzumab as these agents increase the cardiotoxicity because they reduce doxorubicin elimination, resulting in higher plasma levels, and endorse the myocardial metabolism into more toxic metabolites.[30] The oncologist has to separate the infusions and/or limit the cumulative doxorubicin dose to 550 mg/m^2 or use it as a sequential regimen.[30] This approach is only supported by SIOG guidelines.[8]

Replacing doxorubicin with liposomal doxorubicin formulations also reduced toxicity.[31] The evidence-based information is that the liposomal formulations are too big to cross the endothelial linings of the heart, so the free circulating drugs will be limited and may minimize the cardiotoxicity.[4] The problem is that the tumour microenvironment showed the potential for destabilizing the liposomal formula, which leads to degradation of the liposomal formula and release of free doxorubicin.[32,33] ESMO mentioned that liposomal doxorubicin may reduce anthracycline cardiotoxicity, but this is not supported by high-level evidence.[10]

Dexrazoxane is the only drug that has FDA approval as a cardioprotective agent after many childhood and adult clinical studies.[18,34,35] Dexrazoxane is a chelating agent that converts reactive iron that may participate in the cardiotoxicity to inactive iron complexes. Dexrazoxane is licensed in Europe for use in adults with advanced or metastatic breast cancer treated with a doxorubicin cumulative dose of >300 mg/m^2 or those who benefit from continued doxorubicin therapy. Moreover, the clinical use of dexrazoxane is limited as dexrazoxane may interfere with the

antineoplastic activity of doxorubicin and elaborate a negative influence on tumour response.[18] It has been demonstrated that this interference has a negligible clinical effect.[36] Another concern related to dexrazoxane clinical use is increasing the risk of secondary malignancies.[37]

Use of the dexrazoxane strategy was supported by ASCO, ESC, ESMO, NSW and SIOG guidelines. ASCO, NSW recommended this strategy with a doxorubicin dose ≥ 250 mg/m^2 while ESMO, ESC and SIOG recommended doxorubicin dose >300 mg/m^2. This recommendation depends on benefits outweighing harms with intermediate evidence quality. This evidence is supported by three meta-analyses and four clinical trials that evaluated the efficacy of dexrazoxane as a cardioprotective agent in adult cancer patients treated with anthracyclines.[38–43] ASCO referenced the studies by Sepeyer et al., (1992) Venturini et al., (1996), Lopez et al., (1998) and Marty et al.,(2006) indicating that dexrazoxane has a risk reduction in acute clinical and subclinical heart failure. ESMO recommended using dexrazoxane pre-treatment as primary prevention in patients with reduced left ventricular ejection fraction (LVEF >10% to <50%).[41–44] ESC is supporting adding dexrazoxane to doxorubicin in patients with pre-existing clinical heart or significant LV dysfunction depending on two meta-analyses. Cochrane meta-analysis showed a reduction in the risk of heart failure with no difference in chemotherapy efficacy, survival or secondary malignancies between dexrazoxane and control groups. Other meta-analyses showed no differences in secondary malignancy rates for patients treated with dexrazoxane ($p = 0.72$).[37,44,45] We found that the same reference included in ESMO to prove that no malignancy associated with dexrazoxane proves there is a clear association between dexrazoxane and secondary malignancy (41.86 with dexrazoxane versus 10.08 without dexrazoxane, $p = 0.0231$), this discrepancy is due to ambiguous and conflicting results of previous studies, thus more evidence is needed.[37]

Anticoagulant therapy (e.g., dabigatran and apixaban) as prophylactic agent is recommended by ESMO, SEMO and CCS. However, there is limited scientific evidence on the benefit of direct oral anticoagulants in patients treated with chemotherapy.[46] It may be prescribed for patients with a cardiac problem such as atrial fibrillation.[46,47]

CCS, ESC, ESMO, NCCN, NSW and SEMO recommended beta-blockers (β blockers), angiotensin-converting enzyme inhibitors (ACEIs) or/and angiotensin II receptor blockers (ARBs) as prophylaxis while CCS, ESMO, NSW and SEMO recommended them as management of cardiotoxicity induced by doxorubicin. This strategy with cardiovascular drugs such as carvedilol (α1 and β1–2 adrenoceptor blocker), nebivolol (β1 blocker) or carvedilol in combination with enalapril[48] is subjected to the risk versus benefit of adopting this strategy.[49,50]

A reduced degree of protection was documented with metoprolol (β1 blocker) or enalapril alone.[51] Unfortunately, there is no safe and effective drug protocol specific for preventing doxorubicin-induced cardiac toxicity other than the standard therapies currently being utilized for congestive heart failure which include ACEIs, ARBs, beta-blockers and loop diuretics. However, universal primary prevention with standard heart failure medications is controversial, with only a few small studies demonstrating clinical benefit in high-risk populations such as cancer patients with cardiovascular disease and patient showing a persistent troponin increase.[48,52–58]

CCS, ESC, ESMO and SEMO recommended using statins as a prophylactic agent; however, CCS and ESMO considered statin as management in patients with several cardiovascular risk factors (Table 2), although the use of statins remains unclear regarding benefits in the absence of any long-term studies.[59]

The discontinuation decision of doxorubicin for a patient with cardiotoxicity is supported by NSW after multidisciplinary decision by medical treatment team as no evidence to continue doxorubicin despite the cardiotoxicity.[6] While ASCO could not recommended continuation or discontinuation and preferred a collaboration between oncologist and cardiologist balancing the risks and benefits of continuation of therapy and cardiotoxicity induced by doxorubicin. ESMO recommended using cardioprotective agents with close surveillance instead of discontinuation with little harm. ESMO recommended multidisciplinary team from cardiologists, oncologists, haematologists and radiation oncologists to control cardiotoxicity and limiting dose reduction or discontinuation of doxorubicin. [10]

The guidelines supported the healthy lifestyle including a healthy diet and avoidance of hazardous agents that may increase the risk of heart failure or cardiovascular disease (e.g., tobacco or illicit drug use) with physical exercise to control cardiovascular diseases before, during and after chemotherapy. Patient education is highly recommended in most of the guidelines.[60]

Long-term survivors treated with cardiotoxic chemotherapy should be screened to reduce the incidence of heart failure, but agreement does not exist about the optimal test for screening and frequency of testing. Cancer patients at risk for a cardiac problem should undergo close monitoring and be subjected to cardiac screening, including LVEF scan and cardiac enzymes during and after treatment.[47] Prevention and management of cardiotoxicity is based on limited data and the physician's clinical experience.[4]

In summary, after assessing all the guideline recommendations, it was evident that there were several discrepancies. All guidelines agreed that comorbidities, cardiac disease, previous radiotherapy, smoking and cumulative dose were regarded as important risk factors for cardiotoxicity. All the guidelines disagreed on bolus anthracycline administration except for the NSW which stated this as a risk factor to take into consideration. Age was considered as a risk factor but the age range 15–65 years was different amongst the

guidelines. Female gender was also considered as a risk factor amongst guidelines except the SIOG that considered being male as a risk factor. All guidelines considered cumulative dose of doxorubicin as a risk factor, however, CCS and SIOG did not mention the dose range. The value of cumulative dose considered a risk factor was 240–400 mg/m^2. Only ESC considered genetic factor as a risk factor for cardiotoxicity.

This appraisal found that all guidelines supported the history and physical examination as a preventative approach and management of cardiotoxicity. Nevertheless, all guidelines disagreed to antiplatelet prescribing, use of diuretics, and combination of ACE-I/BB (except ESMO) as prophylactic agents against cardiotoxicity. Dexrazoxane as prophylactic agent was supported by CCS, NCCN and SEMO guidelines only.

For management of cardiotoxicity all guidelines agreed to referral to a cardiologist or cardio-oncologist All guidelines supported echocardiogram for monitoring cardiotoxicity, however, all disagreed on endomyocardial biopsy, except ESMO. All guidelines supported using multigated acquisition (MUGA) as monitoring tool except NCCN and SEMO.

Surveillance was varied amongst guidelines i.e., ASCO, ESMO and NCCN recommended this to be done after 6–12 month of doxorubicin administration while ESC advised the surveillance after three months; by CCS and NSW, SEMO and SIOG did not indicate any period for Surveillance

Strength and limitations

To our knowledge, this is the first study that explored the contents and the quality of guidelines for the prophylaxis of doxorubicin-induced cardiotoxicity. A systematic search of literature was performed and supporting evidence was evaluated. The AGREE II instrument, a well-established tool, was used to evaluate the methodology of guidelines.[13] Nonetheless, some recommendations may be missed as some difficulties in identifying some recommendations was experienced as these were involved with other texts and some were not involved in the body of guidelines.

Conclusion

Our result designates that the current guidelines for the prophylaxis and management of doxorubicin-induced cardiotoxicity require improvement. The production of evidence with high quality and the development of evidence-based guidelines are needed for the prophylaxis and management of doxorubicin-induced cardiotoxicity .

Author contributions

IM: contributed to conceptualization of the manuscript, analysis the data of this review and writing of the manuscript.
MV: contributed to conceptualization of the manuscript as well as reviewing and guidance during writing.
VAP: contributed to reviewing the manuscript.
FO: contributed to conceptualization of the manuscript, provided guidance on methodology, as well as reviewing and guidance during writing.

Authors' note

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. All authors reviewed and approved the final version of the manuscript.

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ORCID iD

Iman Moustafa https://orcid.org/0000-0002-9522-7800

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