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PRIMERS IN CARDIO-ONCOLOGY

Cancer Therapy-Related Cardiac Dysfunction of Nonanthracycline Chemotherapeutics

What Is the Evidence?

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ABSTRACT

Cancer therapy-related cardiac dysfunction (CTRCD) is one of the most concerning cardiovascular side effects of cancer treatment. Important reviews within the field of cardio-oncology have described various agents to be associated with a high risk of CTRCD, including mitomycin C, ifosfamide, vincristine, cyclophosphamide, and clofarabine. The aim of this study was to provide insight into the data on which these incidence rates are based. We observed that the reported cardiotoxicity of mitomycin C and ifosfamide is based on studies in which most patients received anthracyclines, complicating the interpretation of their association with CTRCD. The high incidence of vincristine-induced cardiotoxicity is based on an incorrect interpretation of a single study. Incidence rates of clofarabine remain uncertain due to a lack of cardiac screening in clinical trials. The administration of high-dose cyclophosphamide (>1.5 g/m^2/day) is associated with a high incidence of CTRCD. Based on our findings, a critical re-evaluation of the cardiotoxicity of these agents is warranted. (J Am Coll Cardiol CardioOnc 2019;1:280–90) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In recent years, considerable attention by cardiologists and oncologists worldwide has been devoted to decreasing the adverse cardiovascular side effects of cancer treatment. The position paper of the European Society of Cardiology on cancer treatment and cardiovascular toxicity further increased awareness of the discipline cardio-oncology (1). Cardiovascular toxicity of anticancer treatment can manifest itself in various ways, including hypertension, arrhythmias, pericarditis, and coronary artery disease. One of the most concerning side effects is cancer therapy-related cardiac dysfunction (CTRCD), typically defined by declines in left ventricular ejection fraction with or without symptoms of heart failure (HF). The development of CTRCD is dependent on patient-related factors such

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HIGHLIGHTS

- CTRCD is one of the most concerning cardiovascular side effects of anticancer treatment.
- Mitomycin C, ifosfamide, cyclophosphamide, clofarabine, and vincristine are frequently recognized as being highly cardiotoxic, causing CTRCD in ≥10% of patients.
- This primer provides insight into the data upon which the CTRCD incidence rates of these agents have been based.
- A critical re-evaluation of CTRCD rates is necessary because these numbers have been based on data in which most patients received prior or concurrent treatment with other cardiotoxic drugs, including anthracyclines.
- Systematic reviews, meta-analyses, consistent and detailed reporting of cardiovascular toxicity, and international registries are of pivotal importance to establish the cardiotoxicity profile of these chemotherapeutics.

as age and pre-existing cardiovascular disease but also specifically on the chemotherapeutic agent. Anthracyclines are notorious for causing cardiomyocyte damage in a dose-dependent manner. The incidence of doxorubicin-related HF is estimated at 5%, 16%, 26%, and 48% for cumulative doses of 400, 500, 550, and 700 mg/m^2, respectively (2). Patients who develop cardiac dysfunction after anthracycline administration carry a prognosis similar to that of idiopathic dilated cardiomyopathy, with a 5- and 10-year cardiovascular mortality rate of 9% and 24%, respectively (3). Another agent of which CTRCD has been studied extensively is the monoclonal antibody trastuzumab. In contrast to anthracycline-induced cardiac dysfunction, trastuzumab-related cardiac dysfunction is not dose dependent and is reversible in most cases (4).

Because there may be a time-dependent relationship between HF treatment initiation and recovery of cardiac function (5), proper risk stratification is key in facilitating the early detection and treatment of this side effect. In addition to anthracyclines, mitoxantrone, and trastuzumab, recent important review articles within the field of cardio-oncology and the European Society of Cardiology position paper have reported various other chemotherapeutic agents as highly cardiotoxic (i.e., ≥10% incidence of CTRCD) (Table 1). The purpose of this study was to investigate the origin of the currently used incidence rates of CTRCD in these frequently cited articles (Table 1) (1,4,6,7).

ABBREVIATIONS AND ACRONYMS

CTRCD = cancer therapy–related cardiac dysfunction

HF = heart failure

FDA = Food and Drug Administration

MMC = mitomycin C

METHODS

Four landmark review articles within the field of cardio-oncology that reported the incidence of CTRCD were used to identify nonanthracycline agents, which have been described as highly cardiotoxic (i.e., causing CTRCD in ≥10% of patients treated) (1,4,6,7). Agents that were classified as "highly cardiotoxic" in ≥2 of these 4 review articles were included in our subsequent analysis. This resulted in the inclusion of the following 5 chemotherapeutics: mitomycin C (MMC), vincristine, clofarabine, ifosfamide, and cyclophosphamide (Table 1). We thoroughly studied the articles referenced by these review articles and evaluated the incidence rates, definitions of CTRCD, and prior or concurrent use of other known cardiotoxic anticancer agents, including anthracyclines and the anthraquinone mitoxantrone. Additionally, we searched for other trials describing the cardiotoxic side effects of the selected agents. For clofarabine, we performed a systematic published data review using the search term "clofarabine" and applying the filter "clinical trials." This search yielded 98 studies in total, including 13 clinical trials in which clofarabine was used as a first-line agent. For the other agents, it was out of the scope of this primer to perform a systematic review, considering the large body of data published on these agents (MMC, n = 2,100; cyclophosphamide, n ≥ 10,000; ifosfamide, n = 1,636; vincristine, n = 4,499).

RESULTS

MITOMYCIN C. MMC is an alkylating agent that causes cross-linking of DNA and thereby inhibits DNA synthesis. It is used in the treatment of gastrointestinal, genitourinary, and gynecological cancers. Two review articles describe that this chemotherapeutic leads to CTRCD in 10% of patients (4,6), a number that was derived from a study by Verweij et al. (8). Verweij et al. evaluated the incidence of HF in 37 patients treated with MMC and found 1 patient who developed cardiac failure after concomitant treatment with MMC and doxorubicin. This study found a frequency of HF of 10% through pooling of their

TABLE 1 Study Characteristics, Definitions, and Incidence of Cardiovascular Toxicity of Analyzed Studies

Mitomycin C

First Author (Year) (Ref. #)	Dose	Anthracyclines	Nonanthracyclines	Cardiac Screening	Cardiovascular Toxicity Outcome	Sample Size	Incidence, n (%)
Verweij (1988) (8)	Cumulative dose 1-50 mg/m^2	Prior (n = 5) or concurrent doxorubicin (n = 19)	Cisplatin (n = 2)	ECG, MUGA, and TTE before, during, and after treatment	Heart failure; Subclinical cardiotoxicity	24 24	1 (4) 0 (0)
		None			Heart failure; Subclinical cardiotoxicity	13 13	0 (0) 0 (0)
Buzdar (1978) (9)	NA	Prior DOX	NA	NA	Heart failure	91	14 (15)
Creech (1983) (10)	3.5-10 mg/m^2 per cycle; median of 2 cycles	87/90; cases 235-540 mg/m^2 DOX	Prior cyclophosphamide, methotrexate, 5-FU	Baseline ECG	Heart failure	90	4 (4)
Doyle (1984) (11)	10 mg/m^2 per cycle; mean of 3 cycles	DOX 50 mg/m^2 per cycle	None	NA	Heart failure	45	1 (2)
Villani (1985) (12)	10 mg/m^2 per cycle	DOX 45-60 mg/m^2 per cycle; max 500 mg/m^2		TTE before, during, and after therapy	Heart failure	46	6 (13)
Stewart (1983) (13)	10-20 mg/m^2 per cycle; median of 1 cycle	All prior chemotherapy (not specified)	All prior chemotherapy (not specified); metronidazole	NA	Cardiotoxicity	40	0 (0)
Jodrell (1991) (14)	8 mg/m^2 at alternating cycles	MX 8 mg/m^2 per cycle; 6-12 cycles	Methotrexate	ECG and LVEF before and after therapy	Asymptomatic LVEF decline	60	2 (3)
					Heart failure	60	0 (0)
De Forni (1992) (15)	NA	None	5-FU	ECG	Cardiac manifestations (details not specified)	46	0 (0)
Conti (1995) (16)	10 mg/m^2 at alternating cycles	None	5-FU	NA	Cardiotoxicity (details not specified)	28	0 (0)
Seitz (1998) (17)	7 mg/m^2 at alternating cycles	Continuous hepatic artery infusion of pirarubicin (n = 2)	5-FU	NA	Cardiotoxicity (details not specified)	24	0 (0)

Vincristine

First Author (Year) (Ref. #)	Dose	Anthracyclines	Nonanthracyclines	Cardiac Screening	Cardiovascular Toxicity Outcome	Sample Size	Incidence
Brugarolas (1978) (25)	10 weekly doses of 1.5 mg	None	None	NA	Cardiotoxicity (details not specified)	35	0 (0)
Pritchard-Jones (2003) (26)	10 weekly doses of 1.5 mg/m^2	None	None	NA	Cardiotoxicity (details not specified)	242	0 (0)

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results with the results of 4 other clinical trials. The incidence of HF in these latter studies, in which at least 95% of the patients of each study population were also treated with doxorubicin (range 100 to 800 mg/m^2), varied from 2.2% to 15.4% (9–12). All patients who developed HF had been treated with anthracyclines as well, which complicates the interpretation of the true cardiotoxicity of MMC alone. Possible synergistic cardiotoxic effects between doxorubicin and MMC have been suggested by 2 of these studies (9,12). In the largest of these studies (N = 180), 14 of 91 (15.4%) patients treated with MMC and prior doxorubicin developed symptomatic HF compared with 3 of 89 (3.4%) in patients treated only with doxorubicin (9).

The dose-dependent relationship (>30 mg/m^2) with the incidence of CTRCD is also derived from the paper of Verweij et al. (8) and is based on a single patient who developed acute HF after the administration of doxorubicin (150 mg/m^2) and MMC (30 mg/m^2). Other clinical studies evaluating cardiotoxicity with MMC (n = 198) have not described incident HF

TABLE 1 Continued

Clofarabine

First Author (Year) (Ref. #)	Dose	Anthracyclines	Nonanthracyclines	Cardiac Screening	Cardiovascular Toxicity Outcome	Sample Size	Incidence
Relapsed/refractory leukemia							
Jeha (2006) (31)	52 mg/m^2 day 1–5; every 2–6 weeks for up to 12 cycles	Prior treatment with anthracyclines	None	TTE/MUGA before, during, and after therapy	LVEF decline; Heart failure	40 40	7 (18) 1 (3)
Jeha (2009) (32)	52 mg/m2 day 1–5; every 2–6 weeks for up to 12 cycles	Prior treatment with anthracyclines	None	TTE/MUGA before, during, and after therapy	LVEF decline; Heart failure	28 28	9 (32) 2 (7)
First-line treatment							
Löwenberg (2017) (33)	10 mg/m^2 day 1–5; 2 cycles	IDA 12 mg/m^2 day 1–3 in first cycle	Cytarabine, amsacrin	ECG; echo upon indication	CTCAE v4.0; grade II, III, IV	393	NA
Jabbour (2017) (34)	Induction:15 mg/m^2 day 1–5; consolidation: 15 mg/m^2 day 1–3	Induction: IDA 10 mg/m^2 day 1–3; consolidation: IDA 8 mg/m^2 day 1–2; median of 3 cycles	Cytarabine	NA	ELN criteria (≥5%); all grades and grade ≥3	106	NA
Fathi (2016) (35)	30 mg/m^2 day 1–5; 1 cycle	Induction: DOX 30 mg/m^2 day 1–2; consolidation (n = 4): DOX 30 mg/m^2; 8 cycles	Prednisone, vincristine, PEG asparaginase	NA	CTCAE v3.0; grade III + IV + V	17	NA
Willemze (2014) (36)	Induction (1–2 cycles): dose escalating 10–15 mg/m^2 on day 2, 4, 6, 8, and 10	Induction (1–2 cycles): IDA 10 mg/m^2 on day 1, 3, and 5; consolidation: (1 cycle): IDA 10 mg/m^2 on day 4, 5, and 6	Cytarabine	NA	CTCAE v3.0; grade III + IV Cardiac arrhythmia	25	1 (4)
Martinez-Cuadrón (2014) (37)	Induction (1–2 cycles): 20 mg/m^2 day 1–5; early termination of study due to high mortality rate	None	Cytarabine	NA	CTCAE v4.0	11	NA
Escherich (2013) (38)	Consolidation: 40 mg/m^2 day 1–5	Induction (1 cycle): DNR 36 mg/m^2 day 1–4	Prednisolone, vincristine, PEG asparaginase, cyclophosphamide, methotrexate	NA	CTCAE v2.0; grade I + II, III + IV	42	NA
Burnett (2013) (39)	20 mg/m^2 day 1–5; median of 2 cycles	None	None	NA	CTCAE v3.0; grade III + IV	196	20* (10)
Faderl (2012) (40)	Induction: 20 mg/m^2 day 1–5; consolidation (up to 17 cycles; median of 4 cycles in responding patients): 20 mg/m^2 day 1–3	None	Cytarabine, decitabine	LVEF before therapy	Adverse events (>10%); grade I + II, III + IV	60	NA
Burnett (2010) (41)	20–30 mg/m^2 day 1–5; mean 1.6 cycles	None	None	NA	CTCAE v3.0; grade III+IV	106	10 (9)
Kantarjian (2010) (42)	Induction: 30 mg/m^2 day 1–5; consolidation: 20 mg/m^2 day 1–5; median of 2 cycles	None	None	LVEF before therapy	CTCAE v3.0; grade III + IV (>10%)	112	NA
					Acute myocardial infarction	112	2
Faderl (2008) (43)	Induction: 30 mg/m^2 day 1–5; consolidation (median 2–3 cycles): 30 mg/m^2 day 1–3	None	Cytarabine	Serial LVEF assessments (n = 5)	Adverse events (frequency >10%); atrial fibrillation	70	12 (17)
					LVEF decline	5	3 (60)
Faderl (2006) (44)	Induction (max 3 cycles): 40 mg/m^2 day 2–6; consolidation (max 6 cycles): 40 mg/m^2 day 1–3	None	Cytarabine	LVEF before and after therapy	Adverse events	60	NA
Krauter (2018) (45)	Induction (2 cycles): 20–35 mg/m^2 day 1–5	Induction (2 cycles): IDA 7.5mg/m^2 day 1 and 3	Cytarabine	NA	CTCAE v4.0; grade I + II, grade III + IV	42	NA

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TABLE 1 Continued

Ifosfamide

Study	Dose	Anthracyclines	Nonanthracyclines	Cardiac Screening	Cardiovascular Toxicity Outcome	Sample Size	Incidence
Quezado (1993) (46)	2.5–4.5 g/m^2/day during 4 days; 1 cycle	DOX (n = 45) (384 ± 23 mg/m^2); all cases had prior AC	Carboplatin, etoposide, vinblastine, CCNU	NA	Heart failure	52	9 (17)
Antman (1993) (47)	2.5 g/m^2/day during 3 days; median of 3 cycles	DOX 15 mg/m^2 during 4 days; median of 3 cycles	None	NA	Heart failure; grade III + IV, V	170	0 (0)
Sutton (1996) (48)	5 g/m^2/day, once per cycle; max 9 cycles	DOX 50 mg/m^2 per cycle; max 9 cycles	None	NA	Heart failure	34	1 (3)
Becher (1996) (49)	2 g/m^2/day on day 1 and 8; 6–8 cycles	EPI 30 mg/m^2 on day 1 and 8; 6–8 cycles	None	MUGA before and after therapy	Heart failure Δ LVEF pre-post-treatment	349	3 (1) NS Δ LVEF
Elias (1990) (50)	2–4.5 g/m^2/day during 4 days; median of 2 cycles	DOX 344 and 550 mg/m^2 (cases)	None	NA	CTCAE v1.0; grade 2 Heart failure	29	2 (7)
Brade (1991) (52)	NA	None	None	NA	WHO grade II–IV cardiotoxicity	1,508	<1%
Le Deley (2007) (53)	3 g/m^2/day during 4 days; 2 cycles	None	Etoposide	NA	WHO; cardiotoxicity	118	0 (0)

Cyclophosphamide

First Author (Year) (Ref. #)	Dose	Anthracyclines	Nonanthracyclines	Cardiac Screening	Cardiovascular Toxicity Outcome	Sample Size	Incidence
Goldberg (1986) (55)	50 mg/kg/day during 4 days	None	None	No standard screening	Heart failure	80	14 (18)
Braverman (1991) (56)	1,500–1,800 mg/m^2 every day during 2–4 days; 750–900 mg/m^2 twice daily during 4 days	DNR 337 ± 173 mg/m^2 DOX 387 ± 174 mg/m^2	Cytarabine, busulfan, etoposide, carmustine	TTE and ECG before and after therapy	Pericarditis Heart failure	44 44	4 (9) 1 (2)
Gottdiener (1981) (57)	45 mg/kg/day during 4 days	None DNR 180–570 mg/m^2	Cytarabine, 6-thioguanine, carmustine, procarbazine	15/24 No	Heart failure Heart failure	24 8	5 (21) 3 (38)
Appelbaum (1976) (58)	45 mg/kg/day during 4 and 6 days	2/4 cases: DNR 180 and 550mg/m^2	Cytarabine, 6-thioguanine, carmustine	No	Myopericarditis	15	4 (27)
Buja (1976) (59)	45–50 mg/kg/day during 4 days	Cases: DNR 180–370 and 530 mg/m^2	Cytarabine, 6-thioguanine, carmustine, 5-azacytidine	NA	Heart failure-related death	29	2 (7)
Cazin (1986) (60)	45 mg/kg/day during 4 days; 60 mg/kg/day during 2 days; 50 mg/kg/day during 4 days	None DOX 400 mg/m^2 and DNR up to 1,325 mg/m^2	6-thioguanine, cytarabine, CCNU	Echocardiographic follow-up in 12/63; serial ECG analysis in 46/63	Heart failure Heart failure	26 37	8 (31) 11 (30)
Steinherz (1981) (61)	60 mg/kg/day during 2 days; 50 mg/kg/day for 4 days; 50–80 mg/kg/day during 2 days	Prior anthracyclines (n = 27)	Cytarabine	TTE before and after CY therapy	Clinical heart failure Fatal hemorrhagic pancarditis	40 40	5 (13) 2 (5)

*Sum of the occurrence of grade 3 to 4 cardiac events during course 1 and 2 (unclear whether this includes patients who are double counted due to experiencing cardiac events during both courses).

5-FU = 5 fluorouracil; Bid = twice per day; CTCAE = Common Terminology Criteria for Adverse Events; CY = cyclophosphamide; DNR = daunorubicin; DOX = doxorubicin; ECG = electrocardiogram; EPI = epirubicin; ELN = European LeukemiaNet; IDA = idarubicin; LVEF = left ventricular ejection fraction; MMC = mitomycin C; MUGA = multigated acquisition scan; MX = mitoxantrone; NA = not available; NS = nonsignificant; TTE = transthoracic echocardiogram; WHO = World Health Organization.

(13–17). More specifically, in 1 study in which active cardiac screening was performed in 60 patients treated with MMC in combination with methotrexate and mitoxantrone, 2 patients developed asymptomatic left ventricular ejection fraction declines (3.3%) (14).

VINCRISTINE. Vincristine is a vinca alkaloid that has been used since the 1960s. It is an antimitotic agent and disrupts cell division by interacting with tubulin proteins. Vincristine is included in treatment regimens for a variety of malignancies, including hematologic malignancies, primary brain tumors,

sarcomas, and pediatric tumors. The main toxic effect of vincristine is neurotoxicity, most frequently presenting as peripheral neuropathy and sometimes as autonomic neuropathy, affecting blood pressure control and heart rate variability (18,19).

The incidence of CTRCD is reported to be up to 25% in patients treated with this agent (**Table 1**) (4,6). However, this number is derived from an autopsy study by Roberts et al. (20), which described the incidence of cardiac tumors in 196 patients who died of malignant lymphoma. They found cardiac involvement in 48 patients (24%), of whom 5 had clinical manifestations. This study did not report on cardiovascular side effects of treatment with vincristine. Therefore, the suggested incidence of CTRCD of vincristine of 25% may be an incorrect interpretation of this single study. A few case reports referred to by Pai and Nahata (6) have described cardiovascular side effects such as coronary spasm (n = 2) (21,22) and myocardial infarction (n = 2) (23,24).

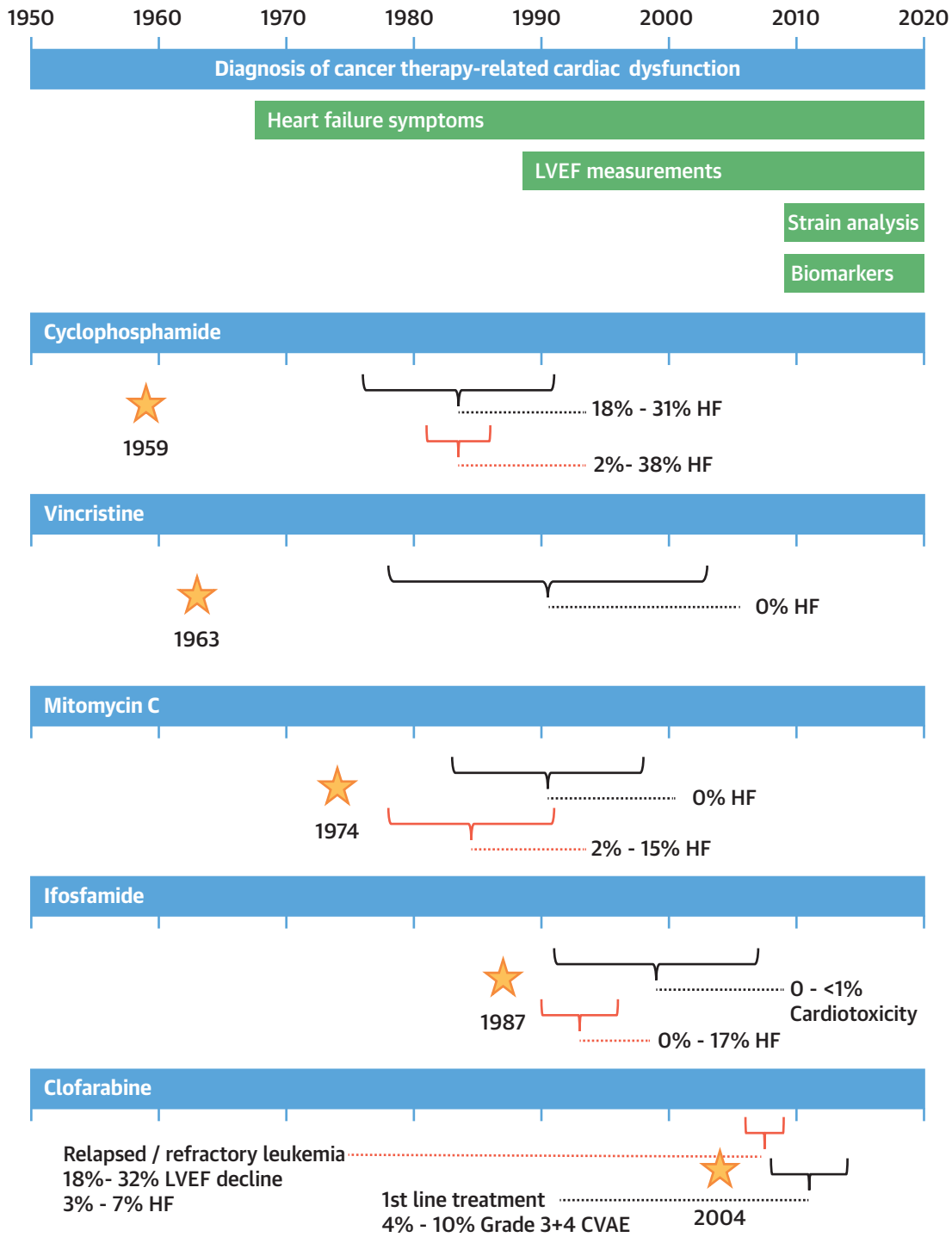
Treatment with vincristine monotherapy is uncommon, which makes it difficult to define the cardiotoxicity risk of this specific agent. Several studies with vincristine monotherapy have not reported any cardiovascular side effects (25,26). It has even been suggested that vincristine may have a protective effect on cardiomyocytes subjected to oxidative stress, which is hypothesized to be the underlying mechanism of anthracycline cardiotoxicity (27,28). This finding was derived from animal studies and has not been reproduced in human studies.

CLOFARABINE. Clofarabine is a relatively new drug that was approved by the U.S. Food and Drug Administration (FDA) in 2004. This purine nucleoside antimetabolite has an antineoplastic effect by directly inhibiting DNA synthesis and ribonucleotide reductase and inducing apoptosis (29). Clofarabine was initially used in patients with recurrent or refractory acute leukemia, and, more recently, it was also incorporated in first-line regimens in patients with acute leukemia. The incidence of left ventricular systolic dysfunction after the administration of clofarabine has been reported to be 27% (15 of 55 patients) (1,4,6,7). This number is derived from the FDA approval letter (30), which described 2 studies of 96 pediatric patients with relapsed or refractory leukemia, all of whom had prior treatment with other potentially cardiotoxic agents (31,32). Cardiac assessment pre- and post-treatment was available in 68 patients. Pericardial effusion was noted in 23 of these 68 patients (34%), although the extent of fluid was limited without any hemodynamic consequences in a majority of the cases. A decrease in left ventricular systolic function was noted in 16 patients (24%), 3 of whom had signs of HF. In some patients, these cardiac changes were transient in nature, although numbers were not specified. Because all patients received prior therapy with other cardiotoxic agents including anthracyclines, the role of clofarabine in provoking these cardiac abnormalities remains unclear.

Although the FDA has recommended serial cardiac assessment during clofarabine treatment, this is not routinely done. In our systematic published data search, we identified only 2 of 13 trials (33–45) that included cardiac screening during and after therapy (43,44). In 1 of these studies, cardiac function was only monitored in 5 of 70 patients (43), and the other study did not report on cardiac outcomes despite active cardiac screening (44). Of the 11 studies that did not perform systematic monitoring of left ventricular function, 3 studies did report on the occurrence of Common Terminology Criteria for Adverse Events grade III to IV cardiac toxicity (arrhythmia, 4% [36]; overall, 10% [39]; overall, 9% [41]). The widespread lack of cardiac screening and the lack of consistent reporting of adverse cardiovascular events in clinical trials with clofarabine might imply that clofarabine is not associated with severe, clinical cardiotoxicity. However, the incidence of subclinical cardiotoxicity including an asymptomatic decline in left ventricular function remains uncertain.

IFOSFAMIDE. Ifosfamide is used in the treatment of hematologic malignancies and sarcomas and belongs to the group of alkylating agents similar to MMC. The incidence of CTRCD is reported to be 0.5% to 17% after ifosfamide administration (1,4,6,7). The highest incidence rate (17%) is based on a study by Quezado et al. (46) in which 9 cases of HF were retrospectively identified from a group of 52 patients who were treated with a single cycle of high-dose ifosfamide (10 to 18 g/m^2/cycle). However, all patients received prior treatment with anthracyclines in doses ranging from 190 to 550 mg/m^2, which raises the question of at least a partial contribution of anthracyclines to the development of CTRCD. A lower incidence of HF (0% to 7%) was found in other studies in patients treated with 4 to 18 g/m^2/cycle of ifosfamide and prior or concurrent anthracyclines (47–51). Ifosfamide therapy without coadministration of anthracyclines is assumed to be

CENTRAL ILLUSTRATION **The Time Span of the Introduction of Chemotherapeutics and the Publication of Their Cardiotoxic Effects**



Kamphuis, J.A.M. et al. J Am Coll Cardiol CardioOnc. 2019;1(2):280–90.

The time span of the introduction of chemotherapeutics (cyclophosphamide, vincristine, mitomycin C, ifosfamide, and clofarabine), methods for the detection of CTRCD, and the publication of their cardiotoxic effects. The brackets represent the time span in which the data were published, with a division between studies in which patients received prior or concurrent anthracyclines **(red brackets)** or treatment without anthracyclines **(black brackets)**. The ranges are derived from the study outcomes from Table 1. The incidence of Common Terminology Criteria for Adverse Events grade 3 and 4 cardiovascular adverse events (CVAEs) of first-line clofarabine treatment was based on only the studies that reported on CVAEs. AC = anthracyclines; HF = heart failure; LVEF = left ventricular ejection fraction.

associated with a low risk of CTRCD (<1%), as was reported in a review of 1,508 patients receiving ifosfamide monotherapy (52) and a randomized trial comparing treatment with doxorubicin to etoposide and ifosfamide (12 g/m^2/cycle) (53). Other cardiac side effects of ifosfamide such as arrhythmias are mainly reversible after discontinuation of the drug (52,54).

CYCLOPHOSPHAMIDE. Cyclophosphamide is an alkylating agent that is used for a variety of malignancies, including breast cancer, lung cancer, lymphomas, and in conditioning regimens before stem cell transplantation. High-dose cyclophosphamide (>1.5 g/m^2/day) is considered to be highly cardiotoxic, with CTRCD incidences ranging from 7% to 28% (1,4,6,7). A single study from Goldberg et al. (55) detected HF in 14 of 80 anthracycline-naive patients after treatment with cyclophosphamide before bone marrow transplantation. HF occurred within 10 days after receiving the first dose of cyclophosphamide and was fatal in 6 of 14 patients. A high daily dose (>1.55 g/m^2) resulted in a greater incidence of HF (13 of 52, 25%) compared with daily doses <1.55 g/m^2 (1 of 32, 3%).

Six studies in which most of the patients had prior treatment with anthracyclines reported an HF incidence that ranged from 2.3% to 30.2% after treatment with high-dose cyclophosphamide (56–61). Cardiotoxic effects, described as HF and myopericarditis, mostly developed within 2 weeks after administration of cyclophosphamide and recovered within days to weeks. However, as noted previously, this was fatal in some cases, with endothelial damage, myopericarditis, and diffuse intramyocardial hemorrhage on postmortem histopathologic examination (57). These histopathological findings differ from those seen in anthracycline-induced cardiotoxicity, which may reflect different mechanisms of cardiotoxicity with this agent.

DISCUSSION

The field of cardio-oncology has made substantial progress in recent years. Nevertheless, there is still a gap in knowledge concerning the cardiotoxic profiles of systemic, nonanthracycline anticancer agents.

First, we observed that CTRCD incidence rates were based on studies that administered these agents as part of combination therapy. Patients typically received prior or concurrent anthracyclines, which makes it difficult to distinguish the true cardiotoxic effect of these chemotherapeutics. Especially for MMC and ifosfamide, the reported high cardiotoxicity rates can likely be attributed to the cardiotoxic effects of anthracyclines.

Second, the 4 review articles report the incidence of CTRCD, which by definition covers both asymptomatic and symptomatic HF. The studies from which these numbers originate mainly report on the incidence of clinical HF. In a majority of cases, these studies do not mention whether active screening of cardiac function was performed. Insufficient monitoring may have led to an under-reporting of asymptomatic decline in left ventricular function. Another limitation in the field is that reviews report incidence rates from studies performed many decades ago (**Central Illustration**). Back then, the diagnosis of CTRCD was predominantly based on signs of clinical HF. More recently, new imaging techniques and biomarkers are used to detect CTRCD in an earlier stage, before the occurrence of clinical HF. Meanwhile, multiple clinical trials within the field of oncology have been performed, providing systematic reports of adverse events. A systematic analysis of the cardiovascular toxicity reported in these trials is likely to provide a more accurate and precise estimate of cardiotoxicity rates of systemic anticancer agents compared with the incidence rates from small, older studies. Recently, a systematic review and meta-analysis on carfilzomib-associated cardiovascular adverse events was published, which provides an excellent example of how the cardiotoxic profile of agents can be analyzed in a comprehensive manner (62).

A majority of clinical trials within the field of oncology report on cardiovascular side effects, without differentiating between arrhythmias, pericardial disease, ischemic heart disease, and myocardial dysfunction. Reporting overall cardiotoxicity does not provide information on the underlying pathologic mechanism, which is important because the different side effects need different approaches to screening, prevention, and treatment. Therefore, it would be important for future clinical trials to provide a more detailed description of cardiovascular adverse effects instead of overall “cardiotoxicity.” Also, reporting whether cardiovascular screening was systematically performed aids in the interpretation of reported side effects because not all adverse effects are overt and may not be evident if screening is not performed. Rigorous reporting standards are likely to advance our understanding of the cardiotoxicity of cancer therapeutics.

STUDY LIMITATIONS. The current study provides insight into the scientific evidence on which the currently used CTRCD incidence rates for these 5 nonanthracycline agents have been based. We believe this study is illustrative of the pitfalls when interpreting cardiotoxicity data. However, for all agents except clofarabine, we did not perform a systematic published data search. In the absence of this, the cardiotoxicity of these chemotherapeutics remains uncertain. Another limitation of this study is that we focused on CTRCD although there are many other cardiovascular side effects of anticancer treatment including arrhythmias and myocarditis. However, we do believe that the findings of this study stress the importance of critically re-evaluating the cardiotoxicity profile of the chemotherapeutics addressed by performing comprehensive published data reviews and meta-analyses. These analyses should not only focus on CTRCD but also evaluate the risk of other types of cardiotoxicity and patient characteristics influencing the susceptibility of developing these treatment-related side effects.

CONCLUSIONS

Our published data search of 5 nonanthracycline anticancer agents, which previously have been recognized to be highly cardiotoxic in landmark review articles, revealed that the reported CTRCD incidence rates for MMC, vincristine, ifosfamide, and clofarabine are based on studies in which many patients received prior or concurrent anthracyclines. This complicates the interpretation of their role in causing CTRCD. We have only found convincing evidence of cardiotoxicity for high-dose cyclophosphamide. Based on our findings, we advise clinicians to take the reference background into account when using the currently reported incidence rates for CTRCD risk stratification. For future studies within the field, we advise that the cardiotoxicity profile of individual agents, and also of antineoplastic regimens as a whole, are needed, particularly when multiple, potentially cardiotoxic agents are combined. Future clinical trials need to provide a more detailed description of cardiovascular side effects instead of overall "cardiotoxicity." Furthermore, international registries need to be developed to collect real-world observational data outside the context of randomized controlled trials.

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REFERENCES

1. Zamorano J, Lancellotti P, Rodriguez Munoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. Eur Heart J 2016;37:2768–801.

2. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;97:2869–79.

3. Fornaro A, Olivotto I, Rigacci L, et al. Comparison of long-term outcome in anthracycline-related versus idiopathic dilated cardiomyopathy: a single centre experience. Eur J Heart Fail 2018;20:898–906.

4. Herrmann J, Lerman A, Sandhu N, Villarraga H, Mulvagh S, Kohli M. Evaluation and management of patients with heart disease and cancer: cardio-oncology. Mayo Clin Proc 2014;89:1287–306.

5. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol 2010;55:213–20.

6. Pai V, Nahata M. Cardiotoxicity of chemotherapeutic agents. Incidence, treatment and prevention. Drug Saf 2000;22:263–302.

7. Yeh E, Bickford C. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol 2009;53:2231–47.

8. Verweij J, Funke-Kupper A, Teule G, Pinedo H. A prospective study on the dose dependency of cardiotoxicity induced by mitomycin C. Med Oncol Tumor Pharmacother 1988;5:159–63.

9. Buzdar A, Legha S, Tashima C, et al. Adriamycin and mitomycin C: possible synergistic cardiotoxicity. Cancer Treat Rep 1978;62:1005–8.

10. Creech R, Catalano R, Shah M, Dayal H. An effective low-dose mitomycin regimen for hormonal- and chemotherapy-refractory patients with metastatic breast cancer. Cancer 1983;51:1034–40.

11. Doyle L, Ihde D, Carney D, et al. Combination chemotherapy with doxorubicin and mitomycin C in non-small cell bronchogenic carcinoma. Severe pulmonary toxicity from 3 weekly mitomycin. Am J Clin Oncol 1984;7:719–24.

12. Villani F, Comazzi R, Lacaita G, et al. Possible enhancement of the cardiotoxicity of doxorubicin when combined with mitomycin C. Med Oncol Tumor Pharmacother 1985;2:93–4.

13. Stewart D, Maroun J, Young V, et al. Feasibility study of combining metronidazole with chemotherapy. J Clin Oncol 1983;1:17–23.

14. Jodrell D, Smith I, Mansi J, et al. A randomised comparative trial of mitozantrone/methotrexate/mitomycin C (MMM) and cyclophosphamide/methotrexate/5 FU (CMF) in the treatment of advanced breast cancer. Br J Cancer 1991;63:794–8.

15. Forni M De, Malet-Martino P, Jaillais P, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. J Clin Oncol 1992;10:1795–801.

16. Conti J, Kemeny N, Saltz L, Andre A, Grossano D, Bertino J. Continuous infusion fluorouracil/leucovorin and bolus mitomycin-C as a salvage regimen for patients with advanced colorectal cancer. Cancer 1995;75:769–74.

17. Seitz J, Perrier H, Giovannini M, Capodano G, Bernardini D, Bardou V-J. 5-fluorouracil, high-dose folinic acid and mitomycin C combination chemotherapy in previously treated patients with advanced colorectal carcinoma. J Chemother 1998;10:258–65.

18. Roca E, Bruera E, Politi P, et al. Vinca alkaloid-induced cardiovascular autonomic neuropathy. Cancer Treat Rep 1985;69:149–51.

19. Hirvonen H, Salmi T, Heinonen E, Antila K, Välimäki I. Vincristine treatment of acute lymphoblastic leukemia induces transient autonomic cardioneuropathy. Cancer 1989;64:801–5.

20. Roberts W, Glancy D, Devita V. Heart in malignant lymphoma (Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma and mycosis fungoides). A study of 196 autopsy cases. Am J Cardiol 1968;22:85–107.

21. Gros R, Hugon V, Thouret J, Peigne V. Coronary spasm after an injection of vincristine. Chemotherapy 2017;62:169–71.

22. Cargill R, Boyter A, Lipworth B. Reversible myocardial ischaemia following vincristine containing chemotherapy. Respir Med 1994;88:709–10.

23. Mandel E, Lewinski U, Djadetti M. Vincristine-induced myocardial infarction. Cancer 1975;36:1979–82.

24. Somers G, Abramov M, Witter M, Naets J. Myocardial infarction: a complication of vincristine treatment? Lancet 1976;2:690.

25. Brugarolas A, Lacave A, Ribas A, Garcia Miralles M. Vincristine (NSC 67574) in non-small cell bronchogenic carcinoma. Results of a phase II clinical study. Eur J Cancer 1978;14:501–5.

26. Pritchard-Jones K, Kelsey A, Vujanic G, Imeson J, Hutton C, Mitchell C. Older age is an adverse prognostic factor in stage I, favorable histology Wilms' tumor treated with vincristine monochemotherapy: a study by the United Kingdom Children's Cancer Study Group, Wilm's Tumor Working Group. J Clin Oncol 2003;21:3269–75.

27. Chatterjee K, Zhang J, Honbo N, Simonis U, Shaw R, Karliner J. Acute vincristine pretreatment protects adult mouse cardiac myocytes from oxidative stress. J Mol Cell Cardiol 2007;43:327–36.

28. Chatterjee K, Zhang J, Tao R, Honbo N, Karliner J. Vincristine attenuates doxorubicin cardiotoxicity. Biochem Biophys Res Commun 2008;373:555–60.

29. Zhenchuk A, Lotfi K, Juliusson G, Albertioni F. Mechanisms of anti-cancer action and pharmacology of clofarabine. Biochem Pharmacol 2009;78:1351–9.

30. FDA. Clolar™ for Intravenous Infustion. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021673s024lbl.pdf. Accessed July 8, 2018.

31. Jeha S, Gaynon P, Razzouk B, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol 2006;24:1917–23.

32. Jeha S, Razzouk B, Rytting M, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute myeloid leukemia. J Clin Oncol 2009;27:4392–7.

33. Löwenberg B, Pabst T, Maertens J, et al. Therapeutic value of clofarabine in younger and middle-aged (18-65 years) adults with newly diagnosed AML. Blood 2017;129:1636–45.

34. Jabbour E, Short NJ, Ravandi F, et al. A randomized phase 2 study of idarubicin and cytarabine with clofarabine or fludarabine in patients with newly diagnosed acute myeloid leukemia. Cancer 2017;123:4430–9.

35. Fathi AT, DeAngelo DJ, Stevenson KE, et al. Phase II study of intensified chemotherapy and allogeneic hematopoietic stem cell transplantation for older patients with acute lymphoblastic leukemia (ALL). Cancer 2016;122:2379–88.

36. Willemze R, Suciu S, Muus P, et al. Clofarabine in combination with a standard remission induction regimen (cytosine arabinoside and idarubicin) in patients with previously untreated intermediate and bad-risk acute myelogenous leukemia (AML) or high-risk myelodysplastic syndrome (HR-MDS): phase I results of an ongoing phase I/II study of the leukemia groups of EORTC and GIMEMA (EORTC GIMEMA 06061/AML-14A trial). Ann Hematol 2014;93:965–75.

37. Martínez-Cuadrón D, Montesinos P, Oriol A, et al. Phase II trials to assess the safety and efficacy of clofarabine in combination with low-dose cytarabine in elderly patients with acute myeloid leukemia. Ann Hematol 2014;93:43–6.

38. Escherich G, zur Stadt U, Zimmermann M, et al. Clofarabine in combination with pegylated asparaginase in the frontline treatment of childhood acute lymphoblastic leukemia: a feasibility report from the CoALL 08-09 trial. Br J Haematol 2013;163:240–7.

39. Burnett AK, Russell NH, Hunter AE, et al. Clofarabine doubles the response rate in older patients with acute myeloid leukemia but does not improve survival. Blood 2013;122:1384–94.

40. Faderl S, Ravandi F, Huang X, et al. Clofarabine plus low-dose cytarabine followed by clofarabine plus low-dose cytarabine alternating with decitabine in acute myeloid leukemia frontline therapy for older patients. Cancer 2012;118:4471–7.

41. Burnett AK, Russell NH, Kell J, et al. European development of clofarabine as treatment for older patients with acute myeloid leukemia considered unsuitable for intensive chemotherapy. J Clin Oncol 2010;28:2389–95.

42. Kantarjian HM, Erba HP, Claxton D, et al. Phase II study of clofarabine monotherapy in previously untreated older adults with acute myeloid leukemia and unfavorable prognostic factors. J Clin Oncol 2010;28:549–55.

43. Faderl S, Ravandi F, Huang X, et al. A randomized study of clofarabine versus clofarabine plus low-dose cytarabine as front-line therapy for patients aged 60 years and older with acute myeloid leukemia and high-risk myelodysplastic syndrome. Blood 2008;112:1638–45.

44. Faderl S, Verstovsek S, Cortes J, et al. Clofarabine and cytarabine combination as induction therapy for acute myeloid leukemia (AML) in patients 50 years of age or older. Blood 2006;108:45–51.

45. Krauter J, Fiedler W, Schlenk FR, et al. Phase I/II study on cytarabine and idarubicin combined with escalating doses of clofarabine in newly diagnosed patients with acute myeloid leukaemia and high risk for induction failure (AMLSG 17-10 CIARA trial). Br J Haematol 2018;183:235–41.

46. Quezado Z, Wilson W, Cunnion R, et al. High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. Ann Intern Med 1993;118:31–6.

47. Antman K, Crowley J, Balcerzak S, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol 1993;11:1276–85.

48. Sutton G, Blessing J, Malfetano J. Ifosfamide and doxorubicin in the treatment of advanced leiomyosarcomas of the uterus: a Gynecologic Oncology Group study. Gynecol Oncol 1996;62:226–9.

49. Becher R, Kloke O, Hayungs J, et al. Epirubicin and ifosfamide in metastatic breast cancer. Semin Oncol 1996;23:28–33.

50. Elias A, Eder J, Shea T, Begg C, Frei E, Antman K. High-dose ifosfamide with mesna uroprotection: a phase I study. J Clin Oncol 1990;8:170–8.

51. Brade WP, Herdrich K, Varini M. Ifosfamide-pharmacology, safety and therapeutic potential. Cancer Treat Rev 1985;12:1–47.

52. Brade W, Herdrich K, Kachel-Fischer U, Araujo C. Dosing and side-effects of ifosfamide plus mesna. J Cancer Res Clin Oncol 1991;117:164–86.

53. Le Deley M, Guinebretière J, Gentet J, et al. SFOP OS94: a randomised trial comparing preoperative high-dose methotrexate plus doxorubicin to high-dose methotrexate plus etoposide and ifosfamide in osteosarcoma patients. Eur J Cancer 2007;43:752–61.

54. Kandylis K, Vassilomanolakis M, Tsoussis S, Efremidis A. Ifosfamide cardiotoxicity in humans. Cancer Chemother Pharmacol 1989;24:395–6.

55. Goldberg M, Antin J, Guinan E, Rappeport J. Cyclophosphamide cardiotoxicity: an analysis of dosing as a risk factor. Blood 1986;68:1114–8.

56. Braverman A, Antin J, Plappert M, Cook E, Lee R. Cyclophosphamide cardiotoxicity in bone marrow transplantation: a prospective evaluation of new dosing regimens. J Clin Oncol 1991;9:1215–23.

57. Gottdiener J, Appelbaum F, Ferrans V, Deisseroth A, Ziegler J. Cardiotoxicity associated with high-dose cyclophosphamide therapy. Arch Intern Med 1981;141:758–63.

58. Appelbaum F, Strauchen J, Graw R, et al. Acute lethal carditis caused by high-dose combination chemotherapy: a unique clinical and pathological entity. Lancet 1976;307:58–62.

59. Buja L, Ferrans V, Grow R. Cardiac pathologic findings in patients treated with bone marrow transplantation. Hum Pathol 1976;7:17–45.

60. Cazin B, Gorin N, Laporte J, et al. Cardiac complications after bone marrow transplantation. A report on a series of 63 consecutive transplantations. Cancer 1986;57:2061–9.

61. Steinherz L, Steinherz P, Mangiacasale D, et al. Cardiac changes with cyclophosphamide. Med Pediatr Oncol 1981;9:417–22.

62. Waxman AJ, clasen S, Hwang WT, et al. Carfilzomib-associated cardiovascular adverse events: a systematic review and meta-analysis. JAMA Oncol 2018;4:e174519.

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