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Anthracyclines in the treatment of early breast cancer friend or foe?

Ana Tecic Vuger [a], Katsuki Tiscoski [b,c], Thiago Apolinario [d], Fatima Cardoso [e,*]

[a] Breast Cancer Department, Division for Medical Oncology, University Hospital for Tumors, Sestre Milosrdnice UCC, Zagreb, Croatia
[b] Department of Clinical Oncology, Santa Casa Misericordia Porto Alegre, Porto Alegre, Brazil
[c] Post-Graduation Program in Pathology, Federal University of Health Sciences of Porto Alegre (UFCSPA), Brazil
[d] Department of Clinical Oncology, Institute of Integral Medicine Professor Fernando Figueira, Recife, Brazil
[e] Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal

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ABSTRACT

Standard chemotherapy for early breast cancer consists generally of an anthracycline – taxane - based regimen, preferably in sequence. Anthracyclines are among the most active cytotoxic drugs against breast cancer. Nevertheless, benefits attained by the use of the more potent anthracycline schedules must be balanced against increased short – and long – term toxicity, and treatment options must be individualized for each patient. Authors review available data regarding anthracycline efficacy and toxicity in the early breast cancer setting and the potential directions for future research.

Introduction

Anthracyclines are widely appreciated in the treatment of cancer due to their powerful antineoplastic effect. Molecularly speaking, their mechanism of action includes DNA intercalation, membrane binding, free radical formation and cell death [1]. First *in vitro* activity was demonstrated 70 years ago by identification of daunorubicin from actinomyces [2]. Years later, the first clinical trials with these agents were reported. Anthracyclines entered breast cancer clinical practice following results of the NSABP B-11 trial, in which the addition of doxorubicin to melphalan and fluorouracil demonstrated improvement in disease free survival (DFS) in early breast cancer (eBC) [3]. When the NSABP B-15 trial compared doxorubicin plus cyclophosphamide (AC) to CMF (cyclophosphamide, methotrexate and fluorouracil), although not demonstrating statistically significant difference in DFS and overall survival (OS), anthracyclines were chosen as preferable, due to shorter duration of treatment, less visits, shorter duration of antiemetic usage, and therefore became standard of care in treatment of eBC [4]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis conducted in 2012 demonstrated that anthracycline - based regimens (with addition of taxanes) compared with no chemotherapy decreased the 10-year risk of breast cancer (BC) recurrence by one third and BC mortality by 20–25% [5]. Although anthracyclines represent an important component of adjuvant chemotherapy, they are associated with several short and long term adverse events, with the major being cardiotoxicity and secondary leukemia [6,7]. In an attempt to attenuate these toxicities, analogs with less toxic features were developed, like pegylated liposomal doxorubicin, which is today an important option for advanced breast cancer [8,9], although still only in clinical trials for the eBC setting. The other idea was to find a predictive biomarker, which could help selecting the patients for whom anthracyclines would provide the major benefit and thus keeping the benefit/risk ratio optimal. Best known attempts were studies of anthracyclines in patients with HER2 overexpression, amplification and possible deletion of the TOP2A gene, and chromosome 17 centromeric duplication, but the results for majority of markers tested remain inconclusive [10,11]. Third idea was to try substituting anthracyclines by other cytotoxics, without compromising the efficacy. Many trials over the years have explored this idea but yielded no definite conclusion. Moreover, several additional questions emerged, the most important related to the possible differential benefit of anthracyclines according to breast cancer biological subtype. In this paper we discuss the most relevant trials addressing the issue of substituting anthracyclines in the treatment of different subtypes of eBC.

Methods

A literature search was performed through the databases EMBASE, PUBMED and COCHRANE, by using the key terms "chemotherapy", "early breast cancer", anthracyclines". We included all trials that tested anthracyclines in the eBC setting and then manually searched the cross –

* Corresponding author. Breast Unit, Champalimaud Clinical Center, Av. De Brasília s/n, 1400-038, Lisbon, Portugal.
E-mail address: fatimacardoso@fundacaochampalimaud.pt (F. Cardoso).

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Table 1
Trials in HR positive or negative and HER2 not tested, positive or negative eBC.

Trial	Year	Study details	Inclusion criteria	Patient characteristics	Primary endpoint	Secondary endpoint	Median FU, mo	Study arms	No.	Outcomes			
										iDFS/DFS/RFS		OS	
USOR 9735 Jones et al. [12]	2009	Phase III; Superiority	Stage I-III	HR +: 71% HR -: 29% HER2 +: 5% HER2 -: 12% HER2 NR: 83%	DFS and OS	DFS by age <65 *v* ≥ 65, toxicity, DFS by HR status	84 m	AC x 4	510	75%	HR 0.74, 95% CI 0.56–0.98, P = 0.033	82%	HR 0.69, 95% CI 0.50–0.97, P = 0.032
								TC x 4	506	81%		87%	
CALGB 49907 Muss et al. [15]	2009	Phase III; Non-inferiority	≥65 y; T > 1 cm	HR +: 32% HR -: 68% HER2 +: 10% HER2 -:75% HER2 NR: 15%	RFS	OS, toxicity, QoL, Functional status	29 m	EC x 4 or CMF x 6	326	89%	HR 2,09, P < 0.001	93%	HR: 1.85, P = 0.02
								Cape x 6	307	80%		88%	
CALGB 40101 Shulman et al. [14]	2014	Phase III; Non-inferiority	ER + pN0 ≥ 1 cm; ER-; pN1	HR + : 68% HR -: 32% HER2 + : 8% HER2 -: 40% HER2 NR: 52%	RFS	OS	73 m	AC or ACdd[a] x 4/6	1931	91%	HR 1.26, one sided 95% UCB 1.48	95%	HR 1.27, one sided 95% UCB 1.56
								Tw or Tdd[a] x 4/6	1940	88%		94%	
ICE II-GBG 52 von Minckwitz et al. [16]	2015	Phase II	>65 yo; pT1/2, pN0/1 high risk or pT3/4 pN2/3.	HR+: 65% HR -: 18% HER2 + : 17% HER2 -: 83%	Compliance and toxicity	Predictive value of geriatric tools for safety and compliance, iDFS, OS	22.8 m	EC x 4 or CMF x 6	198	89%	HR 0.91, 95% CI 0.49–1.71, P = 0.776	94.4%	HR 1.18, 95% CI 0.52–2.66, P = 0.699
								nPx + Cape x 6	193	90.6%		93.7%	
DBCG 07-READ Ejlertsen et al. [13]	2017	Phase III; Non-inferiority	TOP2A-normal operable BC; pN0 high- risk; pN+	HR + :72% HR -: 28% HER2 +: 11% HER2 -: 89%	DFS	OS, DDFS	69 m for DFS; 71 m for OS	EC x 3 - D x 3	1001	87%	HR 1.00, 95% CI 0.78–1.28, P = 1.00	95%	HR 1.15, 95% CI 0.83–1.59, P = 0.41
								TC x 6	1011	88%		94%	

Abbreviations: AC, doxorubicin + cyclophosphamide; TC, docetaxel + cyclophosphamide; EC, epirubicin + cyclophosphamide; CMF, cyclophosphamide + metotrexate + fluorouracil; Cape, capecitabine; dd, dose-dense; T, paclitaxel; w, weekly; nPx, nab-paclitaxel; D, docetaxel; DFS, disease-free survival; OS, overall survival; RFS, relapse-free survival; iDFS, invasive disease-free survival; DDFS, distant disease-free survival; QoL, quality of life; UCB: upper confidence bound.

[a] = trastuzumab was permitted for women with HER2 positive disease.

Table 2
Trials in HR positive or negative and HER2 negative eBC.

Trial	Year	Study details	Inclusion criteria	Patient characteristics	Primary endpoint	Secondary endpoints	Median FU, mo	Study arms	No.	Outcomes			
										iDFS/DFS/RFS[a]		OS	
HORG Mavroudis et al. [23]	2016	Phase III; Non-inferiority	pN+	HR+: 71% HR-: 29% pN1: 64% pN2: 27% pN3: 9%	DFS	OS, Toxicity	FEC-D 46 m; TC 47 m	FECdd ×4 - Ddd x 4	326	89.5%	HR 1.14, 95% CI 0.71–1.83, P = 0.568	NR	HR 1.15, 95% CI 0.49–2.72, P = 0.738
								TC x 6	324	91.1%		NR	
ABC trials Blum et al. [24]	2017	Phase III; Non-inferiority	pN+; pN0 TNBC or ≥ pT2; RS high risk or G3 if T1c HR+	HR + : 69% HR -: 31% pN0: 41% pN1: 44% pN2: 12% pN3: 4%	iDFS	RFI, OS	39.6 m	TaxAC	2062	90.7%	HR 1.23, 95% CI 1.01–1.50, P = 0.04	95%	HR 1.08, 95% CI 0.82–1.41, P = 0.60
								TC x 6	2094	88.2%		94,6%	
WSG PlanB Nitz et al. [25]	2019	Phase III; Non-inferiority	pT1-pT4c and pN+; pN0 high risk (≥pT2, G ≥ 2, HR -, <35 yo, PAI-1 high expression)	HR + : 82% HR -: 18% pN0: 59% pN1: 34% pN2: 5,5% pN3: 1,6% RS ≤ 25 : 48% RS > 25 : 17% RS HR + not tested: 17%	DFS	OS, dRFI, Safety	60 m	EC x 4 – D x 4	1227	89.8%	HR 1.00, 95% CI 0.77–1.29 P = NR	94,5%	HR 0.93, 95% CI 0.65–1.34 P = NR
								TC x 6	1222	89.6%		94,7%	
MASTER trial Yu et al. [26]	2021	Phase III; Non-inferiority	pT1-3 pN+; pT2-3 pN0 high risk (G ≥ 2, LVI +, ≤35 yo, TNBC)	HR + : 92% HR -: 8% pN0: 59% pN1: 34% pN2: 5,5% pN3: 1,6%	DFS	DDFS, OS, Safety.	66 m	TC x 6	524	85%	HR 1.05, 90% CI 0.79–1.39 P = 0.048	96.5%	HR 0.96, 90% CI 0.58–1.59 P = 0.893
								EC x 4 – Tw x 12	524	85.9%	1 (ref)	95.4%	1(ref)
								FEC x 3 – D x 3	523	85.1%	HR 0.99, 90% CI 0.75–1.30 P = 0.045	94.9%	HR 0.84, 90% CI 0.51–1.37 P = 0.549

Abbreviations: FEC, fluorouracil + epirubicin + cyclophosphamide; D, docetaxel; dd, dose-dense; TaxAC, taxane + doxorubucin + cyclophosphamide; TC, docetaxel + cyclophosphamide; EC, epirubicin + cyclophosphamide; T, paclitaxel; w, weekly; DFS, disease-free survival; OS, overall survival; iDFS, invasive disease-free survival; RFI, recurrence-free interval; dRFI, distant recurrence-free interval; DDFS, distant disease-free survival.

[a] = values from the primary endpoint.

Table 3
Trials in HR positive or negative and HER2 positive eBC.

Trial	Year	Study details	Inclusion criteria	Patient characteristics	Primary endpoint	Secondary endpoints	Median FU, mo	Study arms	No.	Outcomes					
										pCR		iDFS/DFS/EFS[a]		OS	
BCIRG 006 Slamon et al. [27,28]	2011	Phase III; Superiority	pT1-3, pN0-3	HR +: 54% HR -: 46% pT1: 40% pT2: 54% pT3: 6% pN0: 29% pN1: 38% pN2: 23% pN3: 10%	DFS	OS, Safety	65 m	AC x 4 – D x 4	1073	–	–	75%	1 (ref)	87%	1 (ref)
								AC x 4 – DH x 4 → H to 1 y	1074	–	–	84%	HR 0.64, P < 0.001	92%	HR 0.63, P < 0.001
								DCbH x 6 → H to 1 y	1075	–	–	81%	HR 0.75, P = 0.04	91%	HR 0.77, P = 0.04
TRYPHAENA Schneeweiss et al. [31,32]	2013; 2018	Phase II	T2-4d, N0-3	HR + : 51% HR -: 49%	Cardiac safety	pCR, DFS, PFS, OS	61 m	FECHP x 3 → DHP x 3	72	50,6%	– –	87%	95% CI 79-95	94%	95% CI 89-100
								FEC x 3→ DHP x 6	75	45,3%	–	88%	95% CI 80-96	94%	95% CI 89-100
								DCbHP x 6	76	52%		90%	95%CI 82-97	93%	95% CI 87-99
APT trial Tolaney et al. [29,30]	2015; 2019	Phase II	pT ≤ 3 cm, pN0 or N1 (mic)	HR + : 67% HR -: 33% pT1: 91,1% pT2 (≤3 cm): 8,9%; pN0:98,5%; pN1mic:1,5%	iDFS	RFI, BCSS, OS	78 m	Tw x 12 + H 1 y	406	–	–	93,3%	95% CI 90.4–96.2	95%	95% CI 92.4–97.7
TRAIN-2 van Ramshorst et al. [33,34]	2018; 2021	Phase III; Superiority	Stage II or III	HR + : 58% HR -: 42% cN-: 36% cN+: 64%	pCR	EFS, OS, toxicity	48 m	FEC-HP 3 → TCbHP x 6	219	67%	95% CI 11–8 P = 0.95	92.7%	HR 0.90, 95% CI 0.50–1.63 P=NR	97.7%	HR 0.91, 95% CI 0.35–2.36 P=NR
								TCbHP x 9	219	68%		93,6%		98.2%	
neoCARH trial Gao et al. [35]	2021	Phase II; Superiority	Stage II or III	HR + : 50% HR -: 50% cN0: 35% cN+: 65%	pCR	EFS, DFS, OS, Safety	66 m	EC x 4 – DH x 4	67	37.3%	OR 2.26, 95%CI 1.09–4.8 P = 0.032	NR	NR	NR	NR
								DCbH x 6	68	55.9%		NR		NR	

Abbreviations: AC, doxorubicin + cyclophosphamide; D, docetaxel; H, trastuzumab; Cb, carboplatin; FEC, fluorouracil + epirubicin + cyclophosphamide; P, pertuzumab; T, paclitaxel; w, weekly; DFS, disease-free survival; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; iDFS, invasive disease-free survival; RFI, recurrence-free interval; BCSS, breast cancer specific survival; EFS, event-free survival.

[a] = values from the primary or secondary endpoints.

Table 4
Trials in TNBC.

Trial	Year	Study details	Inclusion criteria	Patient characteristics	Primary endpoint	Secondary endpoints	Median FU, mo	Study arms	No.	Outcomes					
										pCR		DFS		OS	
NeoSTOP Sharma et al. [39]	2020	Phase II	Stage I (>1 cm), II or III	cT1: 19%, cT2: 70%, cT3-4: 11% cN0: 70% cN+: 30% BRCAm: 17%	pCR	RCB, toxicity, EFS, OS (exploratory)	38 m	TCbw x 4 - ACdd x 4 DCb x 6	48 52	54% 54%	95% CI 40-69 95% CI 40-68	NR NR	NR	NR	NR
PATTERN Yu et al. [38]	2020	Phase III; Superiority	Stage I-III	pT1: 54% pT2-3: 46% pN0: 74% pN+: 26% BRCAm: 10%	DFS	DDFS, RFS, OS	62 m	TCb x 6 FEC x 3 - D x 3	325 322	– –	– –	86.5% 80.3%	HR 0.65, 95% CI 0.44–0.96 P = 0.03	93.4% 89.8%	HR 0.71, 95% CI 0.42–1.22 P = 0.22
Li et al. [44]	2020	Phase III; Superiority	pN + or High-risk fac (<35 y, G3, IAL)	pT1: 42% pT2-4: 58% pN0: 63% pN+: 37% BRCAm: NR	DFS	OS, Toxicity	57 m	ECdd x 4 – Tdd x 4 TCbdd x 8	73 70	– –	– –	79.1% 93.9%	HR 0.31, 95% CI 0.13–0.70 P = 0.005	92.9% 98.5%	HR 0.14, 95% CI 0.06–0.82 P = 0.028

Abbreviations: T, paclitaxel; Cb, carboplatin; w, weekly; D, docetaxel; FEC, fluorouracil + epirubicin + cyclophosphamide; EC, epirubicin + cyclophosphamide; dd, dose-dense. pCR, pathologic complete response; RCB, residual cancer burden, EFS, event-free survival; DFS, disease-free survival; DDFS, distant disease-free survival; RFS, relapse-free survival.

references of the selected papers. We eliminated the trials not directly addressing the question. We ended up selecting 18 trials. Some of the selected trials are direct comparisons of anthracyclines versus non-anthracycline regimens, with a noninferiority or superiority design. The other trials are indirectly giving useful information on the results obtained by a non-anthracyclines regimen in the treatment of eBC. The endpoints used to derive a conclusion are the ones used throughout the studies – DFS, OS and the surrogate endpoint pCR for the neoadjuvant trials.

Results

Early trials testing the possibility of omitting anthracyclines in treatment of eBC

In this analysis we presented four groups of trials testing the possibility of omitting anthracyclines in the treatment of eBC (Tables 1–4). The first group comprises of the trials that included all comers, i.e. patients with any eBC subtype. (Table 1). It is important to note that HER2 testing was still not established as a standard at the time some of the trials were conducted, while HR status was usually used as stratification factor. Among the representative trials in this section, there are two trials testing the superiority of either anthracyclines or non-anthracyclines, and three trials investigating the non-inferiority of the non-anthracyclines regimen [12–16]. Of note, only the USOR 9735 trial showed statistically significant positive result for DFS and OS for non-anthracycline regimen over anthracyclines (DFS 81% TC *v* 75% AC; $P = 0.033$; hazard ratio [HR], 0.74; 95% CI 0.56 to 0.98; OS 87% TC *v* 82% AC; $P = 0.032$; HR, 0.69; 95% CI, 0.50 to 0.97), regardless of age, nodal status and receptor status, even in the longer follow –up period [12,17]. However, the regimen used as comparator in this trial (four cycles of AC) is considered by many a suboptimal treatment regimen, since the best results were obtained when using a sequence of anthracyclines and taxanes [5]. Closer to that idea, Ejlertsen and colleagues conducted the DBCG07-READ trial comparing the non-anthracyclines regimen with the protocol consisting of the entire sequence, anthracyclines and taxanes, and hypothesizing superiority of the sequential protocol [13]. This trial failed to demonstrate any overall outcome benefit from the anthracycline-containing regimen, and with worse toxicity profile. Anthracyclines derived better results in well differentiated tumors and postmenopausal patients, whereas the non-anthracyclines regimen just the opposite. It should be also stated that, following the data on anthracyclines greater benefit in the TOP2a altered cases [18,19], this trial evaluated the anthracycline contribution only in the TOP2A normal cases. The CALGB 40101 trial was designed to demonstrate noninferiority of single agent paclitaxel in comparison to AC regimen [14], based on the good results of taxane monotherapy in the metastatic setting. Noninferiority was not demonstrated in this trial for the primary end point of relapse-free survival (RFS), showing HR of 1.26 (one sided 95% UCB, 1.48) and there was no subgroup in which clinical outcome was different than the overall conclusion of the study. The last two trials, CALGB 49907 trial and ICE II-GBG 52 tested the omission of anthracyclines for older breast cancer patients. The CALGB 49907 did not prove the non-inferiority of mono-chemotherapy with capecitabine, when compared to standard chemotherapy regimens used at that time (EC x 4 or CMF x 6). The HR for recurrence in the capecitabine group was twice that in the standard – chemotherapy group (HR 2.09 $P < 0.001$) [15]. Moreover, quality of life with capecitabine was not substantially different and therefore did not justify its use over standard chemotherapy [20]. The ICE–II–GBG 52 trial was similar to the capecitabine trial, and tested the combination of a taxane and capecitabine [16]. However, the phase II study demonstrated higher toxicity and led to the decision not to proceed to a phase 3 trial.

Trials addressing the omission of anthracyclines in the HER2 negative eBC subtype

Following the idea of de-escalating chemotherapy in lower risk cases, and data on anthracyclines deriving special benefit in the HER2 positive eBC [3,21,22], the trend of testing the non-anthracyclines regimens continued within the HER2 negative eBC population (Table 2). The regimen docetaxel and cyclophosphamide (TC) did not clearly prove to be non-inferior, when compared to the standard sequence regimen of anthracyclines and taxanes in a Greek trial [23]. However, the comparator arm in this trial was a dose dense protocol, which probably impacted the results, and both regimens showed excellent 3-year outcomes for node positive eBC, with DFS 89.5% and 91.1% for the FEC – D and TC arm, respectively (HR 1.147, 95% CI 0.716–1.839, P = 0.568). On the basis of the above mentioned USOR 9735 trial [12], a joint analysis of three similar trials was conducted, again testing the non-inferiority of the TC regimen in comparison to any of the anthracycline – taxane sequential regimen variants in HER2 negative eBC [24]. In more than 2000 patients included in this joint efficacy analysis, the noninferiority of the TC regimen could not be demonstrated. Moreover, results of the ABC trials showed statistically significant improvement in IDFS with the administration of anthracyclines in these patients, the 4-year IDFS was 88.2% for TCx6 and 90.7% for TaxAC ($P = 0.04$) [24]. Additional follow-up time will be useful to fully interpret the data. Another large international randomized program of trials evaluating an anthracycline-free regimen (TC) versus a conventional taxane-AC in HER2 negative eBC, is the WSG Plan B trial, unique because it was conducted in patients who were candidates for chemotherapy according to either clinical or genomic risk criteria [25]. In contrast to the ABC trials' results, the Plan B trial demonstrated excellent 5- year outcomes in both arms, without any statistically significant difference (DFS was 89.6% *v* 89.9%, HR 1, 95%CI 0.77–1.29, P=NR and OS was 94.5% *v* 94.7%, HR 0.93, 95%CI 0.65–1.34, P=NR). It is important to note however, that this trial provides strongest evidence in patients with lower risk disease (i.e. pN0-1), and it does not address the value of dose-dense regimens in high-risk eBC. Also, it has limited power to quantify subtype-specific effects, and that limitation might actually explain the lack of anthracycline benefit in triple negative eBC, observed in this trial, in contrast to what was seen in the ABC trials. A recently published Chinese trial demonstrated non-inferiority of both a non-anthracycline regimen (TC) and a short term anthracycline containing regimen (CEF – T), as compared to what is considered the standard of carre (EC – P) [26]. This trial has some similarities to the Plan B trial, but with higher disease stage of included cases. It is also first study supporting the use of an alternative anthracycline-based regimen. However, it was a single center trial run in an exclusive Asian population and therefore extrapolation to other populations should be done with caution.

Trials omitting anthracyclines in the HER2 positive eBC

Despite the benefit showed by anthracycline-containing regimen in the treatment of HER2 positive eBC, a significant increase in cardiotoxicity was observed among patients treated with anthracyclines and trastuzumab, leading to the need to explore alternative approaches (Table 3). One of the most important trials in this setting is the BCIRG006 trial, in which the non-anthracycline regimen consisted of a taxane combined with a platinum compound, due to the observed preclinical synergies between trastuzumab and platinum salts or docetaxel [27]. This trial was designed to prove the superiority of adding trastuzumab to chemotherapy in treating HER2 positive disease, and, as secondary endpoint, to prove the superiority of the non-anthracycline regimen as compared to the anthracycline arm. The superiority of the non-anthracycline arm was not proven and the trial was not powered to prove non-inferiority between the treatment arms. The 10-years follow-up final results of the trial confirm no significant efficacy difference between the two chemotherapy arms but no proven non-inferiority of the non-anthracycline arm. In terms of toxicity, the non – anthracycline regimen had significantly lower incidence of severe cardiotoxicity (0.4% vs 2.0% seen with anthracycline – containing – trastuzumab –containing regimen), as well as double less of asymptomatic LVEF (left ventricular ejection fraction). Leukemia was higher in ACT regimen, 6 cases, and the non – anthracycline group just one case [28]. Staying in the postoperative setting, another important trial is the adjuvant paclitaxel – trastuzumab trial (APT trial), conducted with the idea of finding an optimal regimen for small node-negative cases [29]. Although noncomparative, single – arm trial, APT demonstrated very low risk of early recurrence among patients with predominantly stage I disease. With the seven years of follow – up, the trial demonstrated excellent long term outcomes, with iDFS 93,3% (95%CI 90.4–96.2%), and OS 95% (95%CI 92.4–97.7%) [30]. In the neoadjuvant setting, it is worth to mention the TRYPHAENA trial [31]. It was designed to primarily evaluate cardiotoxicity of dual HER2 blockade combined with standard chemotherapy regimens, either with or without the anthracyclines, and with no intent to evaluate superiority of any arm. However, it did provide an additional information on non-anthracycline regimen being a good partner to anti HER2 therapy, with high rates of treatment response [32]. Other neoadjuvant trial examining the role of anthracyclines was the TRAIN2 trial [33], that evaluated the additional benefit of incorporating 3-weekly anthracycline regimen in the neoadjuvant treatment course of stage II–III HER2 positive eBC, in the presence of dual HER2 blockade. Superiority of anthracyclines was not proven. Toxic profile was somewhat different, with neutropenia and cardiotoxicity attributed more to anthracyclines, but with no difference in incidence of neuropathy, an adverse effect severely affecting quality of life of patients. Major criticisms to the trial are the low number of patients, none of the used regimens is considered standard of care, and the use of a surrogate endpoint (pCR) as primary outcome, which precludes any definite conclusions regarding the value of anthracyclines for this subtype of eBC. Nevertheless, TRAIN2 trial indisputably adds to the robustness of data in search of response to the question of anthracyclines, and the very recently published updated results confirm the aforementioned first analysis [34]. Finally, a Chinese trial was conducted, in order to assess optimal neoadjuvant chemotherapy regimen in the presence of antiHER2 monotherapy and demonstrated statistically significant higher rates of pCR with the non-anthracycline regimen (55.9 vs. 37.3%) and similar toxicity in both arms [35]. This trial has the same pitfalls as TRAIN2: low number of patients and use of pCR as primary endpoint; in addition, there is also short follow-up.

Trials in triple negative eBC

In last group of trials, we describe information on the triple negative early breast cancer (TNBC) subtype (Table 4). An important proportion of data on the role of anthracyclines in TNBC comes from additional analyses of the earlier mentioned trials. Subgroup analysis of USOR 9735 and the ABC trials' analysis showed bigger benefit of anthracyclines for the TNBC subgroup, while the WSG Plan B demonstrated no additional benefit in comparison to non-anthracycline regimens in this same subgroup [12,24,25]. Building on the biological rationale and information obtained with neoadjuvant trials showing benefit of adding platinum salts in the treatment of TNBC [36,37], the PATTERN trial was designed [38], aiming at proven superiority of a platinum – taxane regimen over an anthracycline – taxane sequential regimen. The results indicate greater benefit of the platinum-based regimen, in terms of DFS, distant DFS, as well as relapse – free survival. However, it is a monoethnic study, analysis of BRCA ½ positive subgroup was underpowered and therefore noninformative, the regimen used is not what is today considered to be standard of care, and the trial predominantly enrolled patients with lower stage disease. Therefore, results must be interpreted with caution. The NeoSTOP trial demonstrated similar efficacy in terms of treatment response and survival outcomes, more favorable toxicity

profile and lower cost of docetaxel – carboplatinum regimen, in comparison to four – drug regimen, including anthracyclines and taxanes in the sequence, when applied as neoadjuvant strategy for stage I-III TNBC [39]. Yet, NeoSTOP is a small phase II trial, not designed as a non-inferiority study, and conducting large prospective phase IIItrials to further support this finding is nowadays not considered a priority in view of the changing landscape of TNBC and the development of other treatment strategies such as immunotherapy and targeted therapy [40,41]. Nevertheless, even from those trials it is still possible to collect an, indirect but useful, information on anthracycline role. When looking at three contemporary neoadjuvant trials incorporating immunotherapy together with chemotherapy, two trials containing anthracyclines in the treatment sequence are the ones deriving higher response rates in general, as well as when immunotherapy was added, and showing positive results in the long term outcomes [40,42]. On the other hand, a trial without anthracyclines had in general lower response rates, and derived no additional benefit when immunotherapy was added (NeoTRIPaPDL, NCT02620280). Eventually, the fact that this trial included a higher risk population may have contributed to the lower pCR rate. As said, these trials represent the trials of new era, investigating new approaches and new agents, particularly the benefit of immunotherapy in TNBC. Their results may suggest the role of anthracyclines as possible important inducers of immunotherapy response, due to their immunomodulatory properties, as already observed in the metastatic setting [43]. Finally, a Chinese trial published in 2020 advocates for possibility of omitting anthracyclines in TNBC, by demonstrating superiority of a platinum – taxane containing adjuvant regimen [44]. Results are obtained in both, lower and higher risk population, irrespective of BRCA 1/2 status. Nevertheless, low number of patients and short follow – up period in the trial precludes from a certain and uniform conclusion, although the trial highlights the role of a platinum component for treatment of TNBC. In conclusion, carboplatin-based regimens in TNBC demonstrated significant improvement in pCR, their effect on long-term outcome is still controversial and their short and long-term toxicities are a concern. The carboplatin-arm in Brightness trial showed higher rates of grade $\geq$3 neutropenia (53% vs 3%), anemia (17% vs 0%), but fortunately similar rates of febrile neutropenia (1% vs 0%), peripheral sensory neuropathy (0% vs 3%) and delivered dose of paclitaxel (88% vs 92%). The 4-year follow-up of the same trial did not demonstrate a significant difference in myelodysplastic syndromes, acute myeloid leukemia, or other second malignancies between the arms [45]. The toxicity profile of the anthracycline-free regimens is different, especially because of the higher doses of taxanes used, with more concerns about peripheral neuropathy. The PATTERN trial showed a fourfold increased risk of neuropathy for the carboplatin arm (3,7% vs 0,9%), although the absolute difference is small [38]. The recognition of different toxicity patterns is very important for the individualization of treatment.

Toxicity of anthracyclines

As already mentioned, the most common and acute side effects of anthracyclines include alopecia, nausea, vomiting, and hematological toxicities, such as leukopenia and neutropenia. These symptoms are reversible and manageable [46,47]. The long-term toxicities such as cardiotoxicity and secondary leukemia are the greater concern. Anthracyclines can accumulate in the mitochondria of myocardial cells, leading to endomyocardial interstitial fibrosis and vacuolation [48]. Acute cardiotoxicity induced by anthracyclines is rare, transient and dose-independent. It is characterized by arrhythmias, electrocardiogram changes, pericarditis, and myocarditis [49]. These changes are observed from the start of infusion or in the first few days after treatment [48]. Late cardiac toxicity is dose-dependent and increases dramatically at doses higher than doxorubicin 400 mg/m 2 or epirubicin 800 mg/m2 [50]. It varies from an asymptomatic drop of left ventricular ejection fraction (LVEF) to clinically relevant heart cardiac failure. The frequency is low (approx. 1%–3%) but it is a serious and life-threatening event [46,51]. Risk factors for anthracycline-induced cardiotoxicity include age (>65 years), higher cumulative anthracycline dose, mediastinal radiation, pre-existing cardiac disorders, and other cardiac risk factors (i.e., hypertension) [52]. Later hematological disorders are acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). The risk of developing is directly related to administered dose and is about 1% [48].

Biomarkers

Retrospective studies suggested that patients with HER 2 amplification or overexpression could derive a higher benefit from anthracyclines [10]. The reason would be that one of the mechanisms of anthracyclines is the blockade of topoisomerase II, and TOP2 and HER2 are closely situated in the arm of chromosome 17 [53]. One of the studies to show this benefit was the DBCCG 89D trial, which evaluated patients with eBC after surgery. Approximately 11% of patients had HER 2 amplification or overexpression and when treated with replacement of methotrexate with epirubicin (CMF vs CEF) had improved recurrence-free survival (RFS) (HR = 0.43, 95%CI 0.24–0.78) and overall survival (OS) (HR = 0.57, 95%CI 0.29–1.13) [54]. However, an important meta-analysis that evaluated five trials regarding the topic showed that the benefit of anthracyclines includes patients with or without HER 2 overexpression/amplification in terms of either EFS (P = 0.0513) or OS (P = 0.1608), with no evident difference between the cohorts [10]. Another biomarker explored was chromosome 17 centromeric duplication (Ch17CE). The comparison between anthracycline-based chemotherapy with CMF in a pooled analysis from five adjuvant trials showed benefits in favor of anthracycline in patients who have TOP2A aberration or CEP17 duplication, but not for HER2 amplification [11]. Considering the described data, the idea of biomarkers leading to patients who will derive better/best results when treated with anthracycline – containing chemotherapy, in the cohort of HER2 positive BC, concluded unsuccessful.

Newest data

A patient-level meta-analysis from EBCTCG, presented at 2021 San Antonio Breast Cancer Conference, demonstrated significant reduction in the invasive recurrence risk with the addition of an anthracycline to taxane-based chemotherapy for early breast cancer [55]. The meta-analysis was performed on individual data, from over 18,000 participants of 16 randomized trials that started before 2012. Primary outcomes were recurrence and cause specific mortality analyzed by standard EBCTCG methods. Pooled data revealed significant 15% of further recurrence risk reduction by adding anthracyclines to taxanes, as well as 13% mortality risk reduction. When categorized by design, among trials included there were three trials which drive the overall result of the analysis, and they tested the regimen of six cycles of concurrent anthracycline – taxane (docetaxel) – cyclophosphamide against six cycles of docetaxel – cyclophosphamide chemotherapy on 2469 patients. Recurrence risk was reduced by as much as 42% with addition of anthracyclines, and the absolute risk reduction was 8.7%. The other eight trials included (including 11,386 patients) in the analysis did not demonstrate significant risk reduction with the addition of anthracyclines. However, they compared sequential anthracycline and taxane, leading to a higher cumulative dose of docetaxel plus cyclophosphamide. Regarding toxicity, the analysis did not attribute more cardiovascular toxicity and secondary hematological malignancies to anthracyclines, but authors advocate for the need of longer follow-up [55]. As a conclusion from the authors, the analysis showed, across all included trials, 15% proportional reduction and 2.5% (95%CI 0.9–4.2) absolute reduction at 10 years in the risk of invasive recurrence for addition of anthracyclines to taxanes, versus taxane alone regimens. Greatest proportional reduction was seen in concurrent chemotherapy protocols because in these types of trials a higher cumulative dose of

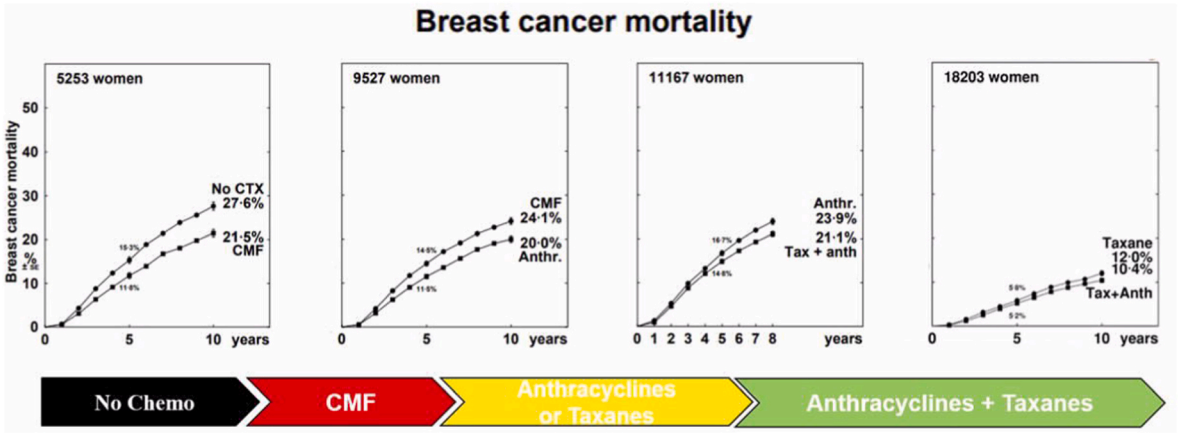

Fig. 1. Breast cancer mortality data adapted from EBCTCG meta-analysis.

both agents than sequential regimens. For this reason, the benefit of adding anthracyclines to taxanes is more clearly seen in concurrent trials where the only difference between arms is the addition of anthracycline to the taxane and cyclophosphamide combination. In contrast, in trials of sequential anthracycline - taxane regimens, where there was a higher dose taxane in the control group, the benefit of adding anthracyclines did not reached significance. Among additional important data to mention, it should be noted that proportional reduction in recurrence did not differ by estrogen receptor status or nodal status, and that very few patients with HER2 positive disease were included in this meta-analysis. To evaluate toxicity and non-breast cancer causes of death a longer follow-up is required [55].

Discussion

All the analyzed data clearly show significant heterogeneity across trials testing the possibility to omit anthracyclines in treating any of the eBC biological subtypes. That precludes us from any certain and strong conclusion. The heterogeneity is mirrored in the design of the trials, included patient population, characteristics of the disease, treatment regimen used as comparator, as well as the investigated regimen, follow up time for the conducted analyses, and the outcomes measured. Furthermore, over time, the idea of dissimilar role of anthracyclines within different breast cancer biological subtype grew, supported by many trials evaluating any specific association of some biological features or biomarkers with the anthracyclines' efficacy. However, not many of those ideas survived the evolution in research and retained significance. On the other hand, new ones, such as the importance of immunomodulatory properties of anthracyclines, are still emerging and currently being tested.

Anthracyclines are clearly one of the most efficacious drugs for breast cancer and their benefit in early breast cancer treatment is nowadays undoubtful (Fig. 1). They are however associated with possible cardiotoxicity and leukemia, important adverse events that cause significant additional morbidity and mortality. In terms of cardiotoxicity, most cases are asymptomatic drops of LEVF, although there are also cases of symptomatic heart failure, some of which may occur several years after the end of treatment. The severe cardiotoxicity is mostly seen with regimens comprising of six cycles of anthracyclines and is less present when only three or four cycles of anthracyclines are used, as it is commonly done in sequential regimens of anthracyclines and taxanes. On the other hand, the leukemia risk may also be attributable, at least partially, to cyclophosphamide used in all standard anthracycline chemotherapy regimens. It is not yet totally clear whether the

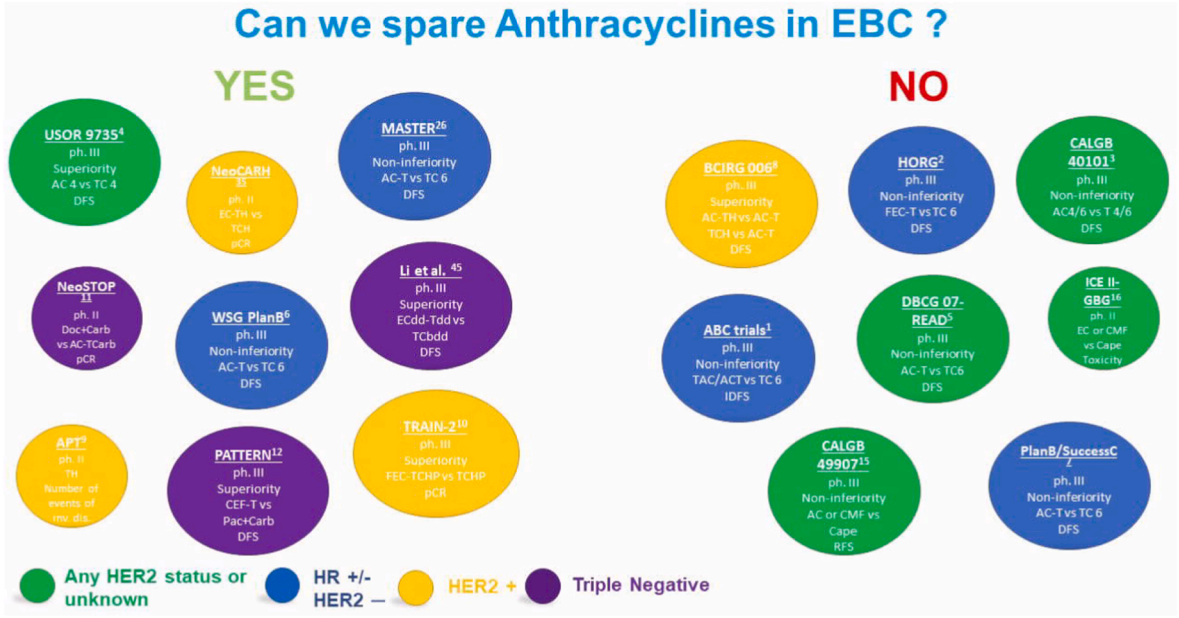

Fig. 2. Trials comparing anthracyclines and non-anthracyclines based regimens.

secondary hematological malignancies developed after breast cancer treatment are due to the alkylating agent, the anthracyclines or the combination.

Conclusion

Considering all data presented and described in the current manuscript, no trial has unequivocally demonstrated superiority of a non-anthracycline regimen in any breast cancer subtype (Tables 1–4, Fig. 2). The trials aiming at proving non-inferiority of a non-anthracycline versus an anthracycline regimen provide a more heterogenous picture (Fig. 2), related to the fact that non-inferiority is always extremely challenging to prove, especially in trials with small to moderate population size. The recent data from the EBCCTG meta-analysis show that regimens with anthracyclines and taxanes are superior to regimens with taxanes alone, in terms of recurrence and mortality. However, heterogeneity in trial design and in particular in dose intensity of the different agents, still raise controversy.

In summary, in our interpretation of the available data anthracyclines and taxanes are needed for the vast majority of TNBC cases, and the addition of platinum and pembrolizumab is justified for intermediate and high risk TNBC. For HER2 positive eBC, we consider that anthracyclines are justified for high risk cases, are controversial for intermediate risk cases and are not justified for low-risk cases, in view of the substantial benefit provided by anti-HER2 therapy, which is the mainstay of treatment for this subtype. For ER positive/HER2 negative eBC, anthracyclines are only justified for high risk luminal-B-like cases, considering the existence of highly efficacious endocrine therapy; the recent data of CDK4/6 inhibitors in the early breast cancer setting adds further complexity. Importantly, differences in efficacy must always be balanced against the risks of toxicity, not just rare and severe side effects but also less severe but persistent toxicities that negatively impact quality of life. Higher cumulative doses of taxanes are associated with higher risk of persistent neuropathy, while higher cumulative doses of anthracyclines are linked to increased risk of cardiotoxicity. It is also crucial to consider the impact of these two classes of agents and of platinum salts on fertility, when managing breast cancer in young women. It is therefore fundamental that patients are well informed about the efficacy and toxicity differences between anthracycline-based and non-anthracycline-based chemotherapy regimens, to be actively involved in treatment decision making. Factors such as co-morbidities, cardiac risk factors, potential impact of persistent neuropathy in the professional life and patients' preferences must always be taken into account. A delicate balance between risk of relapse (based on tumor burden and biology) and risk of severe median and long-term toxicities is necessary for each individual patient. Further research in the field of pharmacogenomics may allow for a better prediction of the risk of specific side effects in the future.

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