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Disease-free survival landmark analysis: a potential critical endpoint in triple-negative breast cancer

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Abstract

Taxanes plus carboplatin (TP) regimen may be an acceptable alternative adjuvant chemotherapy strategy in patients with triple-negative breast cancer (TNBC); however, the difference with the anthracycline-based regimen is yet to be clarified. Therefore, this study aimed to assess the difference between platinum-based and anthracycline-based regimens in prolonging the survival time in TNBC. Using exploratory landmark analysis, we found that the platinum-based TP regimen offers a longer disease-free survival (DFS) than the anthracycline-based regimen in TNBC patients with a DFS of > 4 years.

Keywords: Landmark analysis, Platinum-based, Anthracycline-based, Triple-negative breast cancer, Prognosis

To the Editor,

Breast cancer, as the most common cancer in females, threatens women's health worldwide [1]. Triple-negative breast cancer (TNBC) is a solid malignancy with negative expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2), which accounts for 15%-20% of breast cancer [2]. The anthracycline-based regimen, such as epirubicin plus cyclophosphamide followed by docetaxel or paclitaxel (ECT) regimen, is considered a standard adjuvant chemotherapy regimen and improves survival outcomes of early TNBC [3, 4]. In our previous study, [5] adjuvant carboplatin plus docetaxel or paclitaxel (TP) showed non-inferiority for disease-free survival (DFS)

and overall survival (OS) compared with ECT regimen in TNBC patients.

The platinum-based regimen is an effective alternative adjuvant chemotherapy regimen and is widely used in neoadjuvant chemotherapy for increased pCR rate in patients with TNBC, [4, 6] but it is still unclear whether a platinum-based regimen as adjuvant treatment in TNBC patients has a difference of survival benefit compared with an anthracycline-based regimen. Landmark analysis based on the DFS and OS time can minimize the immortal time bias induced by including events in the hazard model, [7, 8] and provide potential evidence of this difference. Thus, we excavated the landmark analysis aiming to investigate the role of platinum-based adjuvant settings in TNBC patients (ClinicalTrials.gov identifier NCT01150513). The final date of follow-up was January 20, 2021, with a median follow-up of 97.6 months. The Kaplan–Meier method and Breslow test were used to evaluate the prognostic value of early TNBC patients with 2-sided tests set at $P < 0.05$. The landmark analysis was performed using EmpowerStats software (version EmpowerR 2.2, X&Y Solutions, USA).

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Table 1 Clinicopathological features in triple-negative breast cancer patients with a DFS > 4 years (%)

	ECT arm (n = 125)	TP arm (n = 127)	P value
Ages (median [IQR])	48 (42.0—53.0)	48 (42.5—57.0)	0.49
Menopausal status			0.98
Premenopausal	75 (60.00)	75 (59.06)	
Postmenopausal	50 (40.00)	52 (40.94)	
Histological type			0.20
Ductal	117 (93.60)	117 (92.13)	
Lobular	4 (3.20)	1 (0.79)	
Medullary	3 (2.40)	4 (3.15)	
Others	1 (0.80)	5 (3.94)	
Histological grade			0.30
Grade 2	35 (28.00)	25 (19.69)	
Grade 3	78 (62.40)	88 (69.29)	
Missing or unknown	12 (9.60)	14 (11.02)	
Ki67			0.54
< 20%	15 (12.00)	13 (10.24)	
20% ≤ to < 50%	41 (32.80)	43 (33.86)	
≥ 50%	65 (52.00)	70 (55.12)	
Missing or unknown	4 (3.20)	1 (0.79)	
pT			0.35
pT1	67 (53.60)	67 (52.76)	
pT2	56 (44.80)	60 (47.24)	
pT3	2 (1.60)	0 (0.00)	
pN			0.42
pN0	81 (64.80)	93 (73.23)	
pN1	35 (28.00)	29 (22.83)	
pN2	4 (3.20)	3 (2.36)	
pN3	5 (4.00)	2 (1.57)	
pTNM stage			0.53
stage 1	47 (37.60)	50 (39.37)	
stage 2	69 (55.20)	72 (56.69)	
stage 3	9 (7.20)	5 (3.94)	
Intravascular invasion (%)			0.27
Yes	99 (79.20)	110 (86.61)	
No	17 (13.60)	10 (7.87)	
Missing or unknown	9 (7.20)	7 (5.51)	
PD-L1 status			0.16
negative	69 (55.20)	57 (44.88)	
positive	24 (19.20)	24 (18.90)	
Missing or unknown	32 (25.60)	46 (36.22)	
Surgery			0.07
Radical surgery	94 (75.20)	81 (63.78)	
Breast conserving	31 (24.80)	46 (36.22)	

DFS disease-free survival, ECT, docetaxel or paclitaxel followed by epirubicin plus cyclophosphamide, TP docetaxel or paclitaxel plus carboplatin

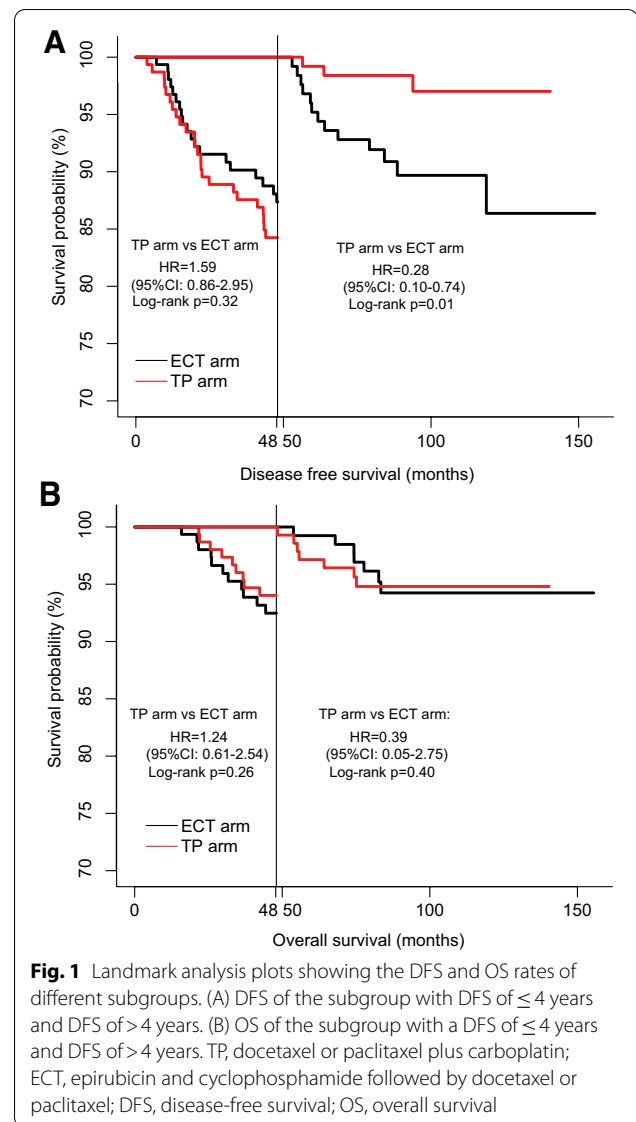


Fig. 1 Landmark analysis plots showing the DFS and OS rates of different subgroups. (A) DFS of the subgroup with DFS of ≤ 4 years and DFS of > 4 years. (B) OS of the subgroup with a DFS of ≤ 4 years and DFS of > 4 years. TP, docetaxel or paclitaxel plus carboplatin; ECT, epirubicin and cyclophosphamide followed by docetaxel or paclitaxel; DFS, disease-free survival; OS, overall survival

Based on our previous study, [5] we enrolled all TNBC patients treated with the TP regimen or the ECT regimen in the landmark analysis at 4 years. For TNBC patients with a DFS of > 4 years, a total of 125 (81.2%) patients in the ECT regimen and 127 (82.5%) patients in the TP regimen were analyzed in the study. TNBC patients (a DFS of > 4 years) were well balanced between the ECT regimen and TP regimen, and the detailed clinicopathological characteristics were seen in Table 1. As shown in Fig. 1, in TNBC patients with a DFS of ≤ 4 years, DFS (HR, 1.59; 95% CI, 0.86–2.95; $P=0.32$; Fig. 1A) and OS (HR, 1.24; 95% CI, 0.61–2.54; $P=0.26$; Fig. 1B) had no

difference between the TP regimen and the ECT regimen. In TNBC patients with a DFS of >4 years, the TP regimen had a longer DFS (HR, 0.28; 95% CI, 0.10–0.74; $P=0.01$) (Fig. 1A) and was not associated with a better OS (HR, 0.39; 95% CI, 0.05–2.75; $P=0.4$) (Fig. 1B) than the ECT regimen.

This is the first landmark analysis assessing the difference in therapeutic effect between a platinum-based regimen and an anthracycline-based regimen as adjuvant treatment in TNBC patients, which showed that the TP regimen seems to have a longer DFS than the ECT regimen with a life expectancy of more than 4 years. The following reason may explain the differences. Firstly, the 5-year DFS rate of the TP regimen in our previous study (84.4%) was almost consistent with that in another study (86.5%) [4]. However, the results in our control group were inconsistent with that in the other study, probably because the ECT regimen administered in our control group was stronger than that of cyclophosphamide, epirubicin plus fluorouracil followed by the docetaxel regimen used in the previous study. Secondly, a recent study showed that high-dose anthracycline-based chemotherapy elicits a state of immunological dormancy and promotes resistance to chemotherapy in ER-negative BC patients (including those with TNBC) receiving adjuvant chemotherapy [9]. Based on the results of a previous study, anthracycline-based ECT regimen may evade chemotherapy by going senescence, leading to TNBC relapsed. Nevertheless, the TP regimen may be a potentially preferred adjuvant chemotherapy regimen for TNBC patients, especially, in whom, for some reason, the standard anthracycline-taxane regimen is not being used.

Abbreviations

TNBC: Triple-negative breast cancer; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor-2; ECT: Epirubicin plus cyclophosphamide followed by docetaxel or paclitaxel regimen; TP: Carboplatin plus docetaxel or paclitaxel; DFS: Disease-free survival; OS: Overall survival.

Acknowledgements

Thanks to all enrolled patients and physicians who participated in the study.

Author contributions

Conception and design: PY and FZ. Acquisition and analysis of data and provided the clinical data: FZ, TW, XW, JY and PY. Writing, review, and/or revision of the manuscript: FZ, TW, XW, FD, JY and PY. Study supervision: PY. All authors read and approved the final manuscript.

Funding

This work was supported by the CSCO Pilot Oncology Research Fund (Y-2019AZMS-0377), National Natural Science Foundation of China (82172650).

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and was also approved by the ethics committees of Cancer Hospital, Chinese Academy of Medical Sciences.

Consent for publication

All authors declare that they have no conflict of interest.

Competing interests

Not applicable.

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Received: 24 May 2022 Accepted: 1 September 2022

Published online: 27 September 2022

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