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Original Article

Real-World Outcome of Platinum-Based Chemotherapy in Advanced Breast Cancer (ABC): A Retrospective Study from a Tertiary Cancer Center in India

Indhuja Muthiah Vaikundaraja[1] Manikandan Dhanushkodi[1] Venkatraman Radhakrishnan[1] Jayachandran Perumal Kalaiarasi[1] Nikita Mehra[1] Gangothri Selvarajan[1] Arun Kumar Rajan[1] Siva Sree Kesana[1] Balasubramanian Ananthi[2] Priya Iyer[2] Manjula Rao[3] Arvind Krishnamurthy[3] Sridevi Velusamy[3] Rama Ranganathan[4] Tenali Gnana Sagar[1]

[1] Department of Medical Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India
[2] Department of Radiation Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India
[3] Department of Surgical Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India
[4] Department of Epidemiology & Biostatistics, Cancer Institute (WIA), Chennai, Tamil Nadu, India

Address for correspondence Manikandan Dhanushkodi, MD, DM, DNB, Medical Oncology, Cancer Institute (WIA), Chennai, 38, Sardar Patel Road, Chennai, Tamil Nadu, 600036, India (e-mail: dmani1982@gmail.com).

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Abstract

Introduction There is a paucity of data on platinum-based chemotherapy in advanced breast cancer (ABC) from developing countries like India.

Objectives The objectives were to analyze the efficacy and safety of platinum-based chemotherapy in patients with ABC.

Materials and Methods This was a retrospective study of 35 patients with ABC who were treated with platinum-based chemotherapy (gemcitabine and carboplatin, [GC]) in a tertiary cancer center in India from August 2015 to November 2019. The inclusion criteria were patients with ABC, who had received palliative chemotherapy with GC. The exclusion criteria were patients who had received less than two cycles of GC and patients who received platinum-based chemotherapy for neuroendocrine carcinoma of the breast.

Results The median age was 45 years (range: 28–68 years). All patients were female (97%) except one male (3%). The histology was ductal carcinoma (77%), mixed (17%), and others (6%). Out of the 12 patients tested for breast cancer (BRCA) gene mutation, six patients had a BRCA mutation. Patients with metastatic and locally progressive disease were 91 and 9%, respectively. The median number of prior lines of systemic therapy for metastatic disease was 1 (range: 0–5). The median number of sites of metastasis was 2 (range: 0–5). Patients with visceral crises were 23%. The median

Keywords
- advanced breast cancer
- platinum-based chemotherapy
- real-world outcome

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number of cycles of GC chemotherapy received was 6 (range: 2–6). A dose reduction in chemotherapy was done in 74%. The responses among 34 evaluable patients were complete response (11%), partial response (24%), stable disease (41%), and progressive disease (24%). Grade 3 or more hematological and nonhematological toxicities were observed in 69 and 9%, respectively. The median progression-free survival and overall survival were 6 and 8 months, respectively. The 1-year progression-free survival and overall survival were 19 and 34%, respectively. Multivariate analysis showed that patients who had received more than 3 cycles had a better outcome.

Conclusion GC was an active and well-tolerated regimen in ABC regardless of the receptor status. Further prospective randomized studies are warranted to assess the optimal regimen in patients with triple-negative breast cancer.

Introduction

Platinum-based neoadjuvant chemotherapy (cisplatin and carboplatin) has been shown to improve pathological complete response in triple-negative breast cancer (TNBC), especially in the breast cancer (BRCA) mutant subtype.[1] Platinum-based chemotherapy (PBC) can be combined with anti-HER2 therapy (trastuzumab) for the treatment of HER2-positive BRCA.[2] The impact of PBC as compared to non-PBC in advanced breast cancer (ABC) is unclear. The chemotherapy drugs that can be combined with platinum include taxane, vinorelbine, etoposide, and gemcitabine.[3] The response rates are higher in the first line as compared to second or third-line therapy.[4] There is a paucity of data on PBC in ABC from developing countries like India. The objectives of this study were to analyze the efficacy and safety of PBC in patients with ABC.

Materials and Methods

This was a retrospective study of 35 patients with ABC who had received palliative chemotherapy with gemcitabine and carboplatin (GC) in a tertiary care cancer center from August 2015 to November 2019. The data were retrieved from the electronic medical records (EMR) of these patients for whom gemcitabine and carboplatin prescription was given. At our hospital, patient records registered from 1954 until 2016, and records of patients who had deceased were scanned. The data of patients for whom case records were scanned were obtained from the EMR. For the alive patients registered after 2016, we obtained data from the individual case record obtained from the tumor registry.

The inclusion criteria were patients with ABC, who had received palliative chemotherapy with GC. The exclusion criteria were patients who had received less than two cycles of GC and patients who received PBC for neuroendocrine carcinoma of the breast. BRCA was tested as per National Comprehensive Cancer Network (NCCN) hereditary BRCA testing criteria[5] and the methodology used was Ion Torrent next-generation sequencing. The primary objective was to assess the progression-free survival (PFS) and overall survival (OS) of patients with recurrent/metastatic BRCA who received palliative chemotherapy with GC while the secondary objective was to assess the toxicity.

Prechemotherapy blood investigations included hemogram, renal function test, and liver function test before the day (D) 1 of each cycle and hemogram and differential count before D8 of each cycle. Chemotherapy was initiated only if the absolute neutrophil count was more than 1000/µL and platelet count was >1 lakh/µL. The premedications were injection palonosetron 0.25 mg intravenous bolus and injection dexamethasone 12 mg intravenous bolus 30 minutes before chemotherapy. The chemotherapy schedule was injection gemcitabine 1 gm/m^2 in 250 mL 0.9% normal saline over 30 minutes intravenously on D1 and D8 and injection carboplatin area under the curve 5 or 6 in 250 mL 0.9% normal saline over 1 hour on D1.

Patients were assessed clinically for response and toxicity before each cycle. Imaging was done with either chest X-ray, ultrasound of abdomen/pelvis, or contrast-enhanced chest tomography of chest/abdomen/pelvis or positron imaging tomography-computed tomography once every 3 to 4 months and when clinically indicated. Responses were assessed as per the Response Evaluation Criteria in Solid Tumors, version 1.1 criteria.[6] Toxicity was graded as per Common Terminology Criteria for Adverse Events, version 4.0.[7] Chemotherapy dose reduction was done in patients with $\geq$ grade 3 toxicity and discontinued in patients with life-threatening toxicity.

Statistical Analysis

Descriptive statistics were used to analyze the baseline characteristics. PFS was calculated from the date of initiation of GC to the date of recurrence or death. OS was calculated from the date of the initiation of GC to the date of death due to any cause. Survival was estimated by the Kaplan–Meier method and compared across groups using the log-rank test. Cox proportional hazard model was used to find the prognostic factors affecting the outcome. All p-values were two-sided, and values <0.05 were considered significant. This was performed using the Statistical Package for the Social Sciences version 15 (SPSS), Chicago, Illinois, United States.

Ethics

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013. The study was approved by the Institutional Ethics Committee of Cancer Institute (WIA), Chennai (IEC/2020/Aug 08), dated Aug 14, 2020 and a waiver of consent was obtained as this was a retrospective study.

Results

Baseline Characteristics

A total of 35 patients were included in this analysis with a median follow-up of 8 months (range: 2–39 months). The median duration from diagnosis to start of GC chemotherapy was 18 months (range: 2–113 months). The median age was 45 years (range: 28–68 years). All patients were females ($n = 34/35$, 97%) except for one male ($n = 1/35$, 3%). Premenopausal women were 76% ($n = 26/35$) and the rest 24% ($n = 8/35$) were postmenopausal. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 1 (83%) and 2 (17%). The histology was ductal carcinoma (77%), mixed (17%), and others (6%). The differentiation was grade 2 (17%) and grade 3 (80%). The molecular subtype was luminal B ($n = 10/35$, 29%), HER2 positive ($n = 6/35$, 17%), and triple-negative subtype ($n = 19/35$, 54%). Two of the six patients with HER2-positive BRCA had received adjuvant trastuzumab. Out of the 12 patients tested for BRCA 1 and 2 gene mutations, six patients had a BRCA 1 mutation. Recurrence was confirmed by biopsy in 37% ($n = 13/35$) patients. Patients with metastatic and locally progressive disease were 91 and 9%, respectively. The median number of prior lines of systemic therapy for metastatic disease was 1 (range: 0–5). The median number of sites of metastasis was 2 (range: 0–5). Patients with visceral crises were 23% ($n = 8/35$). This study included two patients with brain metastasis and one with choroidal metastasis. The baseline characteristics are shown in ►**Table 1**.

Table 1 Baseline characteristics ($n = 35$)

Variable	Number (%)
Median age	45 years (range: 28–68 years)
Sex	
Female	34 (97)
Male	1 (3)
Menopausal status[a]	
Premenopausal	26 (76)
Postmenopausal	8 (24)
Comorbid illness[b]	
Diabetes mellitus	9 (27)
Hypertension	7 (21)
Others	8 (24)
None	18 (54)
ECOG performance status	
0	0 (0)
1	29 (83)
2	6 (17)
3 or 4	0 (0)
Histology	
Infiltrating ductal carcinoma	27 (77)
Mixed	6 (17)
Others[c]	2 (6)
Differentiation	
Grade 1	0 (0)
Grade 2	6 (17)
Grade 3	28 (80)
Unknown	1 (3)
Estrogen receptor	
Positive	13 (37)
Negative	22 (63)
Progesterone receptor	
Positive	8 (23)
Negative	27 (77)
HER2	
Positive	6 (17)
Negative	28 (80)
Unknown	1 (3)
Molecular subtype	
Luminal A (ER/PR positive, HER2 negative & Ki 67 $\leq$ 20%)	0 (0)
Luminal B, HER2 negative (ER/PR positive & Ki 67 $>$ 20%)	10 (29)
HER2 positive	6 (17)
TNBC	19 (54)

(*Continued*)

Treatment, Response, and Toxicity

The median number of cycles of GC chemotherapy received was 6 (range: 2–6). A dose reduction in chemotherapy was done in 74% ($n = 26/35$). The responses were complete response ($n = 4/35$, 11%), partial response ($n = 8/35$, 23%), stable disease ($n = 14/35$, 40%), progressive disease ($n = 8/35$, 23%), and unknown ($n = 1/35$, 3%). The hematological and nonhematological toxicities of $\geq$ grade 3 were observed in 69 and 9%, respectively. Grade 3 or more anemia, leucopenia, and thrombocytopenia were observed in 34, 46, and 37%, respectively. Febrile neutropenia was observed in 9% of patients. Grade 3 or more chemotherapy-induced nausea and vomiting, hypersensitivity, and neuropathy were observed in 3, 3, and 3%, respectively. There was no treatment-related mortality.

Survival

The median PFS (►**Fig. 1**) and OS (►**Fig. 2**) were 6 (95% confidence interval [CI]: 3.2–5.7 months) and 8 months (95%

Table 1 (*Continued*)

Variable	Number (%)
BRCA mutation status	
BRCA 1 or 2 mutation present	6 (17)
Wild type	6 (17)
Unknown	23 (66)
De novo metastatic disease	12 (35)
Recurrent disease	23 (65)
Median number of sites of metastatic disease	2 (range: 0–6)[d]
Visceral crisis	
Yes	8 (23)
No	27 (77)
Median number of lines of prior therapy in metastatic disease	1 (range: 0–5)

Abbreviations: BRCA, breast cancer; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor; TNBC, triple-negative breast cancer.
[a]One male patient was excluded.
[b]Percentage may not add to 100% as patients had combination of comorbid illness.
[c]One patient has metaplastic carcinoma and 1 patient had poorly differentiated carcinoma with neuroendocrine features.
[d]Range starts with 0 as 3 patients had only locally progressive disease.

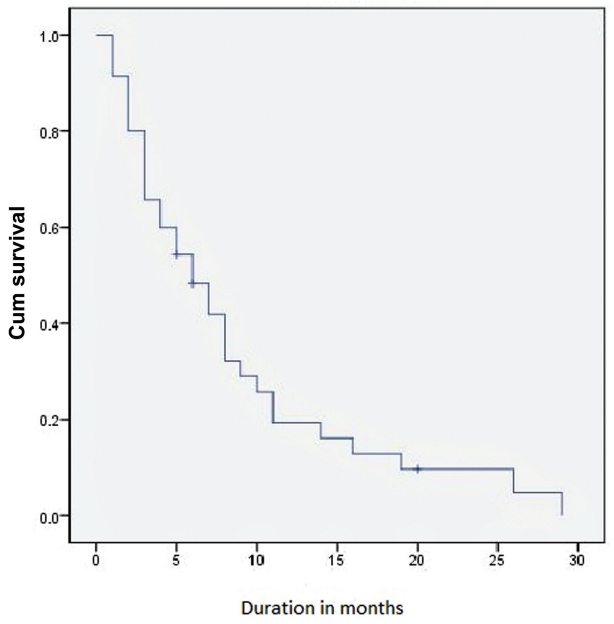

Fig. 1 Kaplan–Meier curve (x-axis: survival in months; y-axis: percentage of patients) of 35 patients with advanced breast cancer treated with gemcitabine–carboplatin showing a median progression-free survival of 6 months (95% confidence interval: 3.2–5.7 months).

CI: 5.3–10.7 months), respectively. The 1-year PFS and OS were 19 and 34%, respectively. Univariate analysis was done with factors including age, menopausal status, histology, molecular subtype, BRCA status, number of lines of prior therapy, number of sites of metastasis, and number of cycles of GC chemotherapy for correlation with PFS. Univariate analysis showed that patients with infiltrating ductal carcinoma histology and those who received more than 3 cycles of chemotherapy had better PFS (►**Table 2**). Multivariate analysis confirmed that patients who had received more than three cycles of chemotherapy had better PFS (hazard ratio: 3.05, 95% CI: 1.36–6.82, $p = 0.007$).

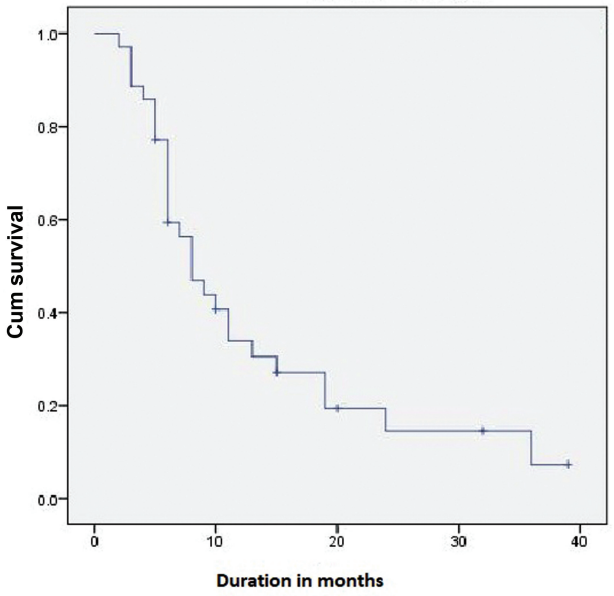

Fig. 2 Kaplan–Meier curve (x-axis: survival in months; y-axis: percentage of patients) of 35 patients with advanced breast cancer treated with gemcitabine-carboplatin showing a median overall survival of 8 months (95% confidence interval: 5.3–10.7 months).

Discussion

This study is the largest study from India on PBC in ABC. The study included real-world patients like those in ECOG PS 2 (17%), HER2 positivity (17%), and pretreated (maximum 5 lines of prior systemic therapy) ABC who were treated with gemcitabine and carboplatin.

Currently, there is no standard chemotherapy option in patients who progress after exposure to anthracycline, taxane, and capecitabine. The chemotherapy options include ixabepilone, vinorelbine, eribulin, and PBC. We chose GC as it was an affordable treatment option.

Germline BRCA testing was done in 12 patients. Among them, 6 patients (50%) had BRCA 1 mutation and none had BRCA 2 mutation. The NCCN guidelines recommend BRCA testing for all patients with a family history of breast or ovarian cancer, age less than 45 years, bilateral BRCA, male BRCA, breast and ovarian cancer, and TNBC less than 60 years of age.

Biopsy confirmation of recurrent disease was done only in 37% due to inaccessible site, patient's unwillingness, and short disease-free survival. All current guidelines including (NCCN), American Society of Medical Oncology, European Society of Medical Oncology, and ABC recommend repeat biopsy from accessible metastatic setting especially in the

Table 2 Univariate analysis with correlation with progression-free survival

Variable	HR	CI (95%)	*p*-Value
Histology			
Infiltrating ductal carcinoma	1.00		
Others	2.40	1.04–5.67	0.04
Molecular subtype			
Luminal B	1.00		
HER2 enriched	1.23	0.33–4.60	0.75
Triple negative breast cancer	1.76	0.79-3.92	0.16
Number of cycles of chemotherapy			
>3 cycles	1.00		
≤ 3 cycles	3.23	1.47–7.06	0.03
Number of sites of metastatic disease			
≤ 2 sites	1.00		
>2 sites	0.88	0.39–1.99	0.76
Number of lines of prior systemic therapy for metastatic disease			
≤ 2 lines	1.00		
>2 lines	0.46	0.16–1.35	0.16
BRCA mutation			
BRCA positive	1.00		
BRCA wild type	0.43	0.10–1.78	0.25

Abbreviations: BRCA, breast cancer; CI, confidence interval; HR, hazard ratio.

first recurrence. Repeat biopsy is useful as it not only confirms the recurrence but also identifies discordance in ER, PR, and HER2 status that can alter systemic therapy.[8] Studies from All India Institute of Medical Sciences, Delhi and Kidwai, Bengaluru have shown a receptor (ER/PR/HER2) discordance of 10 to 20% in recurrent BRCA and can be useful in treatment decisions.[9,10]

A Cochrane database systematic review ($n=9742$) showed that combination chemotherapy had improved response and survival but with increased toxicity.[11] But another Cochrane database systemic review ($n=2317$) showed no difference in OS in patients receiving combination versus sequential single-agent chemotherapy.[12] Currently, we do not have studies comparing GC to carboplatin alone in advanced BRCA.

In our study, dose reduction with GC chemotherapy was seen in 74%. A phase 2 study showed that dose reductions with GC occurred in 60% due to myelosuppression.[13] Although dose reduction happened in two-thirds of the patients, most patients completed all the six cycles of chemotherapy.

A study from Gujarat Cancer Research Institute in 21 patients with TNBC showed a response rate of 72% and the survival details were unreported.[14] There are no further studies on PBC in ABC from India. Our study had a lower overall response rate (34%) as it included pretreated patients with ABC. A retrospective study of patients ($n=375$) with de novo ABC from All India Institute of Medical Sciences, Delhi, showed that hormone-positive subset, good PS (0-1), and oligometastasis had a better outcome. Patients with TNBC and those with liver or brain metastasis had a poor outcome.[15]

A study from Royal Marsden showed that PBC improved response and PFS but not OS in patients with advanced TNBC.[16] The triple-negative (TNT) randomized controlled trial (RCT) in patients with untreated TNBC, carboplatin, and docetaxel had similar response and survival. But in patients with BRCA mutated TNBC, carboplatin had a better response and survival.[17] A phase 3 RCT from China showed that patients treated with GC had a better PFS than gemcitabine-paclitaxel in untreated advanced TNBC.[18] A meta-analysis with three RCTs showed that PBC does not improve PFS in patients with advanced TNBC.[19] Another meta-analysis of 4,625 patients with ABC showed that PBC improved PFS and OS with increased fatigue, hematological, and gastrointestinal toxicity.[20] The details of the studies with PBC in ABC are shown in ►**Table 3**.

In our study, the median PFS and OS were only 6 and 8 months, respectively. This could be due to the inclusion of real-world patients like heavily pretreated subset and HER2-positive patients (who could not afford anti-HER2 therapy). The TNBC and BRCA mutant subtype did not correlate with survival possibly because of the small numbers. GC-based regimen could be considered as first-line regimen in patients with BRCA mutant advanced TNBC and as a third-line regimen after anthracycline and taxane in patients with BRCA wild-type advanced TNBC.

Poly ADP ribose polymerase (PARP) inhibitors (olaparib, talazoparib) had shown to improve response and PFS as compared to non-PBC (capecitabine, eribulin, or vinorelbine) in patients with germline BRCA-mutated advanced BRCA.[21,22] However, the addition of PARP inhibitor (iniparib) to GC chemotherapy did not improve survival in patients with advanced TNBC.[23]

Immunotherapy (atezolizumab) with nab-paclitaxel had shown to improve survival as compared to nab-paclitaxel alone in patients with untreated advanced TNBC, especially the PD-L1-positive subset.[24] Pembrolizumab with chemotherapy (nab-paclitaxel, paclitaxel, gemcitabine + carboplatin) improved PFS as compared to chemotherapy alone in patients with PD-L1-positive (combined positive score ≥ 10) untreated advanced TNBC. Sacituzumab govitecan-hziy is an antibody-drug conjugate that targets the human trophoblast cell-surface antigen 2 (Trop-2) with SN-38 had shown durable responses in patients with heavily pretreated advanced TNBC.[20]

The multivariate analysis showed that patients who received more than three cycles of chemotherapy had an improved PFS. None of the other studies of PBC in ABC had shown a similar correlation. The strength includes the first

Table 3 Studies on platinum-based chemotherapy in advanced breast cancer

Study	Inclusion criteria	Sample size	Design	Response (%)	PFS (mo)	OS (mo)
Our study	ABC	35	Retrospective	34	6 mo	8 mo
Maka et al[14]	TNBC	21	Retrospective	72	–	–
Sirohi et al, UK[9]	TNBC	155	Retrospective	41	6 mo	11 mo
Tutt et al, TNT trial[10]	TNBC	766	Phase 3, RCT, carboplatin versus docetaxel	31 versus 34%	3.1 mo versus 4.4 mo	12.8 mo versus 12 mo
Hu et al. China[11]	TNBC	240	Phase 3, RCT, gemcitabine cisplatin versus gemcitabine paclitaxel	65 versus 49%	7.7 mo versus 6.4 mo	Immature

Abbreviations: ABC, advanced breast cancer; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; TNBC, triple-negative breast cancer.

study with the largest sample size from India on real-world outcomes with PBC in ABC. The limitations include retrospective design, lack of biopsy confirmation of recurrence (63%), and unknown BRCA status (66%). Further prospective randomized studies are warranted to assess the optimal regimen in patients with TNBC.

Conclusion

This study is the largest study from India on PBC in ABC representing the real-world outcome. Patients with ECOG PS 2, HER2 positivity, and pretreated ABC were included in this analysis. GC was an active and well-tolerated regimen in advanced BRCA regardless of the receptor status.

Presentation
This study has not been presented in any meeting.

Registration Number
Not applicable as it is not a clinical trial.

Authors' Contribution
Conception (Indhuja Muthiah Vaikundaraja, Manikandan Dhanushkodi)/acquisition (Indhuja Muthiah Vaikundaraja, Manikandan Dhanushkodi)/analysis (Indhuja Muthiah Vaikundaraja, Manikandan Dhanushkodi, Venkatraman Radhakrishnan, Jayachandran Perumal Kalaiarasi, Nikita Mehra, Arun Kumar Rajan, Gangothri Selvarajan, Siva Sree Kesana, Balasubramanian Ananthi, Priya Iyer, Manjula Rao, Arvind Krishnamurthy, Sridevi Velusamy, Rama Ranganathan, Tenali Gnana Sagar). All authors made substantial contribution toward drafting and final approval and agreed to be accountable on all aspects of the manuscript.

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Conflict of Interest
Nil.

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