Original Study

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Single-Agent Gemcitabine vs. Carboplatin-Gemcitabine in Advanced Breast Cancer: A Retrospective Comparison of Efficacy and Safety Profiles

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Abstract

Gemcitabine or carboplatin-gemcitabine (CG) are commonly used in the treatment of advanced breast cancer. We retrospectively compared the efficacy and safety of these treatment regimens in a heterogeneous patient population. Despite a trend toward a higher rate of objective responses, CG was associated with more frequent adverse events and no evidence of better progression-free survival compared to single-agent gemcitabine.

Background: Single-agent gemcitabine is a moderately effective compound in metastatic breast cancer (mBC) treatment. Carboplatin is frequently used in addition to gemcitabine to improve tumor responses, but with an unclear effect on survival outcomes. In this study we evaluated the antitumor efficacy and safety profiles of gemcitabine and carboplatin-gemcitabine in mBC patients. **Patients and Methods:** We retrospectively collected data on patients treated between April 2012 and February 2018 with gemcitabine 800 mg/m^{2}or carboplatin at an area under the curve of 2 with gemcitabine 800 mg/m^2, given on days 1 and 8 every 21 days. We compared progression-free survival (PFS), objective response rate (ORR), overall survival, and incidence of adverse events (AEs) in the 2 cohorts. **Results:** Of 163 consecutive patients who met the inclusion criteria, 75 received gemcitabine and 88 carboplatin-gemcitabine. Patients in the combination cohort had received a lower number of previous chemotherapy lines (2 vs. 3), and were less likely to have received carboplatin (9 patients [10%] vs. 34 patients [45%]; $P < .0001$). We found no PFS differences in carboplatin-gemcitabine and gemcitabine cohorts (4.24 vs. 4.61 months; adjusted hazard ratio, 0.98; $P = .92$), whereas the combination was associated with a trend toward higher ORR (18 patients [20.4%] vs. 8 patients [10.6%]; $P = .089$) and with significantly higher incidence of Grade 3/4 neutropenia (30 patients [34%] vs. 5 patients [6.6%]; $P < .0001$). **Conclusion:** Using carboplatin in addition to gemcitabine is associated with more hematologic AEs but not with better PFS. Although single-agent gemcitabine remains a treatment option for heavily pretreated mBC patients, finding biomarkers of response to platinum salts might help to identify patients more likely to benefit from carboplatin-gemcitabine.

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Introduction

Breast cancer (BC) is the most common malignancy in women of Western countries, with an estimated number of 234,190 new diagnoses in the United States in 2015 and more than 1 million newly diagnosed cases each year worldwide.[1] Approximately 10% of BC patients have locally advanced or metastatic disease at diagnosis, and approximately 30% of patients with initially early-stage tumors subsequently develop recurrent or metastatic BC (mBC).[2] Despite recent therapeutic advancements, mBC remains an almost invariably deadly disease, and chemotherapy (ChT) still represents a central treatment pillar for patients with triple-negative BC (TNBC), endocrine-resistant hormone receptor (HR)-positive (HR^+) BC or $HER2^+$ BC (in combination with anti-HER2 agents).

Anthracyclines and taxanes are highly active agents against BC, and are frequently used in the (neo)adjuvant treatment setting.[3] Therefore, most BCs recurring after curative therapy have been previously exposed to anthracyclines, taxanes, or both. In these patients, rechallenge with anthracyclines is limited by cumulative, dose-dependent cardiotoxicity,[4] whereas taxane rechallenge might be limited by tumor resistance or residual toxicity (mostly neurological).[5] Therefore, the use of cytotoxic agents that are not cross-resistant with anthracyclines and taxanes is of primary importance for mBC patients who are candidates to receive ChT.

Anthracycline- and taxane-pretreated mBC is potentially sensitive to different chemotherapeutic agents,[6] including capecitabine, vinorelbine, eribulin, nanoparticle albumin-bound (nab)-paclitaxel, gemcitabine (G), carboplatin (C), and cisplatin. However, single-agent treatments have shown relatively limited anticancer activity, with objective response rates (ORRs) ranging between 12% and 41% in the first-line setting and 13.6% to 32% in subsequent lines of therapy.[7-13] Compared with single-agent ChT, ChT combinations are associated with higher ORRs but also with higher incidence of adverse events (AEs); moreover, their effect on progression-free survival (PFS) and overall survival (OS) is still debated.[14]

The antimetabolite G (2′, 2′-difluorodeoxycytidine) is a pyrimidine analogue that inhibits DNA synthesis. When used as a single-agent treatment against mBC, it is associated with an ORR of up to 37% in the first-line setting,[15-19] 26% in the second-line setting,[15,17,18,20-24] and 13% in the third-line setting,[17,18,20-25] with a median time to progression (TTP) of 2 to 8 months.[15-25]

Combinations of G and taxanes or platinum salts have been frequently used to improve its efficacy.[26] In particular, the C-G combination (CG) exploits the synergistic anticancer activity of G, which impairs the synthesis of nucleic acids (DNA, RNA), and C, which damages DNA structure by inducing the formation of DNA adducts. CG is actually considered a valid first- or second-line treatment option for patients with mBC, especially TNBC, and is one control regimen frequently used in randomized studies that investigate new ChT combinations.[27] Although CG is active against anthracycline- and taxane-pretreated mBC, it is associated with relevant hematologic toxicities, and no prospective studies have been performed to compare the efficacy and tolerability profile of CG versus single-agent ChT, including single-agent G.

In this study, we evaluated the efficacy and safety profile of single-agent G and CG in a population of mBC patients consecutively treated at our institution between 2012 and 2018.

Patients and Methods

Study Setting and Inclusion Criteria

This was a monocentric, retrospective, independent study in patients with mBC treated between April 2012 and February 2018 at Fondazione IRCCS Istituto Nazionale dei Tumori (Milan, Italy) with single-agent G or CG. Eligibility criteria were: (1) age $\geq$18 years; (2) pathologically/cytologically confirmed diagnosis of unresectable, locally recurrent or mBC; (3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; (4) treatment with 1 of the following ChT regimens: G at the dosage of 800 mg/m^2 on days 1 and 8 of every 3-week cycle, or CG, given as C at an area under the curve (AUC) of 2 with G 800 mg/m^2, both given on days 1 and 8 of every 3-week cycle (patients with $HER2^+$ disease could receive concomitant trastuzumab); (5) available information about previous treatment(s) for limited-stage and/or advanced disease; (6) available data on patient outcomes, including best tumor response, PFS, and OS; and (7) availability of medical records containing information on treatment-related AEs. Subjects fulfilling all these criteria were evaluated, regardless of tumor biology and line of treatment.

Objectives of the Study

The objective of the study was to compare the antitumor activity/efficacy and safety profiles of G and CG in patients with heavily pretreated mBC in the "real life" setting. The primary study end point was PFS, as defined as the time between treatment initiation and disease progression or death from any cause, whichever came first. For patients who received "maintenance therapy" (endocrine therapy or trastuzumab) after obtaining the best response with G or CG, PFS was defined as the time between ChT initiation and disease progression during the administration of maintenance therapy, or after its discontinuation for any reason, including patient death. ORR, TTP, and OS were secondary end points. ORR was defined as the percentage of patients with a complete response or partial response. TTP was defined as the time between treatment initiation and disease progression. Finally, OS was defined as the time between treatment initiation and death from any cause.

Chemotherapy was administered until disease progression or unacceptable toxicity. For a small proportion of patients in the CG cohort, single-agent G or single-agent C was continued after a variable number of CG cycles for reasons related to treatment tolerability. These cases were annotated separately, and, because these patients continued to receive part of the initial therapy, they were not considered as patients receiving "maintenance" treatment.

Patient data were collected according to the ethical principles for medical research involving human subjects adopted in the Declaration of Helsinki. Patients alive at the time of data collection and/or analysis signed an informed consent for the use of their personal data for research purposes.

Assessment of Efficacy and Safety

Tumor response was assessed every 3 ChT cycles using computed tomography or magnetic resonance imaging, but tumor re-evaluation was anticipated in the case of evolving symptoms or other clinical signs indicative of progressive disease. We used the Response Evaluation Criteria in Solid Tumors, version 1.1 to assess tumor response.[28] Clinically evident lesions were evaluated using

Table 1 Clinical and Tumor Characteristics in the Overall Population and in the G and CG Subgroups

Characteristic	Overall (n = 163; 100%)	G Subgroup (n = 75)	CG Subgroup (n = 88)	*P*
Age, Years				
≥65	54 (33.1)	30 (40)	24 (27.3)	
<65	109 (66.9)	45 (60)	64 (72.7)	.085
ECOG PS				
0	82 (50.3)	41 (54.7)	41 (46.6)	
1	71 (43.6)	28 (37.3)	43 (48.9)	
2	10 (6.1)	6 (8)	4 (4.5)	.51
Tumor Biology				
HR^+	101 (62)	53 (70.6)	48 (54.6)	
$HER2^+$	29 (17.8)	14 (18.7)	15 (17)	
TNBC	33 (20.2)	8 (10.7)	25 (28.4)	**.0178**
Lines of Treatment				
≤3	75 (46)	24 (32)	51 (58)	
>3	88 (54)	51 (68)	37 (42)	**.0092**
Number of Metastatic Sites				
≤1	31 (19)	15 (20)	16 (18.2)	
>1	132 (81)	60 (80)	72 (81.8)	.77
Type of Metastatic Site				
Visceral	127 (77.9)	57 (76)	70 (79.5)	
Nonvisceral	36 (22.1)	18 (24)	18 (20.5)	.59
Synchronous Metastases				
Yes	40 (24.5)	12 (16)	28 (31.8)	
No	123 (75.5)	63 (84)	60 (68.2)	**.019**
Previous Anthracycline Treatment				
Yes	147 (90.2)	68 (90.7)	79 (89.8)	
No	16 (9.8)	7 (9.3)	9 (10.2)	.85
Previous Taxane Treatment				
Yes	159 (97.5)	74 (98.7)	85 (96.6)	
No	4 (2.5)	1 (1.3)	3 (3.4)	.73
Maintenance Treatment				
Yes	14 (8.6)	1 (1.3)	13 (14.8)	
No	149 (91.4)	74 (98.7)	75 (85.2)	**.0023**

Data are presented as n (%) except where otherwise noted. The *P* value of the χ^2 test assessing the association between each characteristic and the type of treatment received is indicated in the right column of the table. The *P* value of the test is indicated in bold numbers when statistically significant.
Abbreviations: CG = carboplatin and gemcitabine combination; ECOG PS = Eastern Cooperative Oncology Group performance status; G = gemcitabine; HR = hormone receptor; TNBC = triple-negative breast cancer.

physical examination, with every 3 weeks measurement of lesion diameters using callipers.

To assess treatment safety, we recorded all AEs from medical records and blood exams. All AEs were classified according to the common terminology criteria for AEs, version 4.03 of 2010.[29] Hematologic toxicities were reviewed at the moment of data collection from computerized blood sample data. Nonhematologic toxicities were extracted from medical records, where they are regularly annotated during patient visits.

Exploratory Analyses

Because of the retrospective nature of this study, any PFS or OS difference between G- and CG-treated patients might depend on inhomogeneous distribution of meaningful clinical or tumor-related variables, including the number of previous treatment lines in the 2 patient cohorts. To account for the potential effect of these imbalances on the study results, we also evaluated: (1) the proportion of patients previously exposed to C in the G and CG groups; (2) patient PFS during systemic treatment received subsequently, i.e. after tumor progression to G or CG; and (3) OS measured from the documentation of metastatic disease to the date of patient death from any cause.

Statistical Analysis

The χ^2 test was used to study the distribution of individual dichotomous variables (patient- or tumor-related) in the G versus CG groups. We used the test of proportions to compare the ORR and the rate of AEs in the 2 cohorts. PFS and OS were calculated

Table 2 Clinical Outcomes of Patients in the G and CG Cohorts

Regimen	G	CG	*P*
PFS, Months	4.61	4.24	.942
ORR, %	10.6	20.4	.089
TTP, Months	4.61	4.24	.942
OS, Months	13.5	19.1	**.0219**

For progression-free survival (PFS), time to progression (TTP), and overall survival (OS) the *P* value of the log rank test is indicated in the right column. For ORR, the *P* value of the proportion test is indicated. *P* values are shown in bold when statistically significant.
Abbreviations: CG = carboplatin and gemcitabine combination; G = gemcitabine.

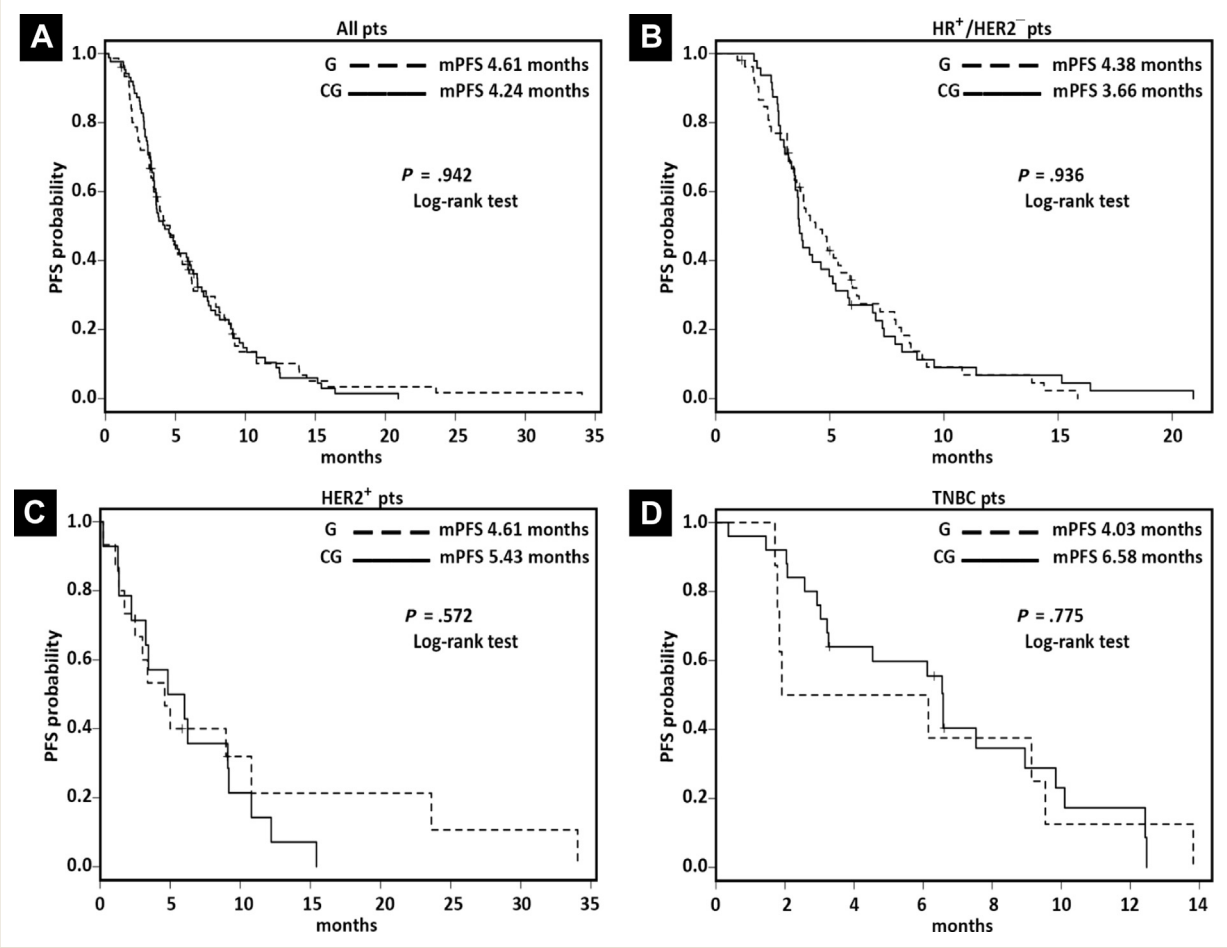
according to the Kaplan–Meier method, and survival curves were compared with the log rank test. Patients who had not progressed or died at the time of data cutoff and analysis were censored at the date of last disease evaluation. The effect of different prognostic factors on PFS and OS was first assessed in univariable analysis. Factors significantly associated with the risk of progression or death ($P < .1$) were included in a Cox proportional hazard model to assess their independent association with survival. A threshold of .05 was set as a significance threshold for other statistical analyses. All statistical analyses were performed using the software R (version 3.3.2; R Institute for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

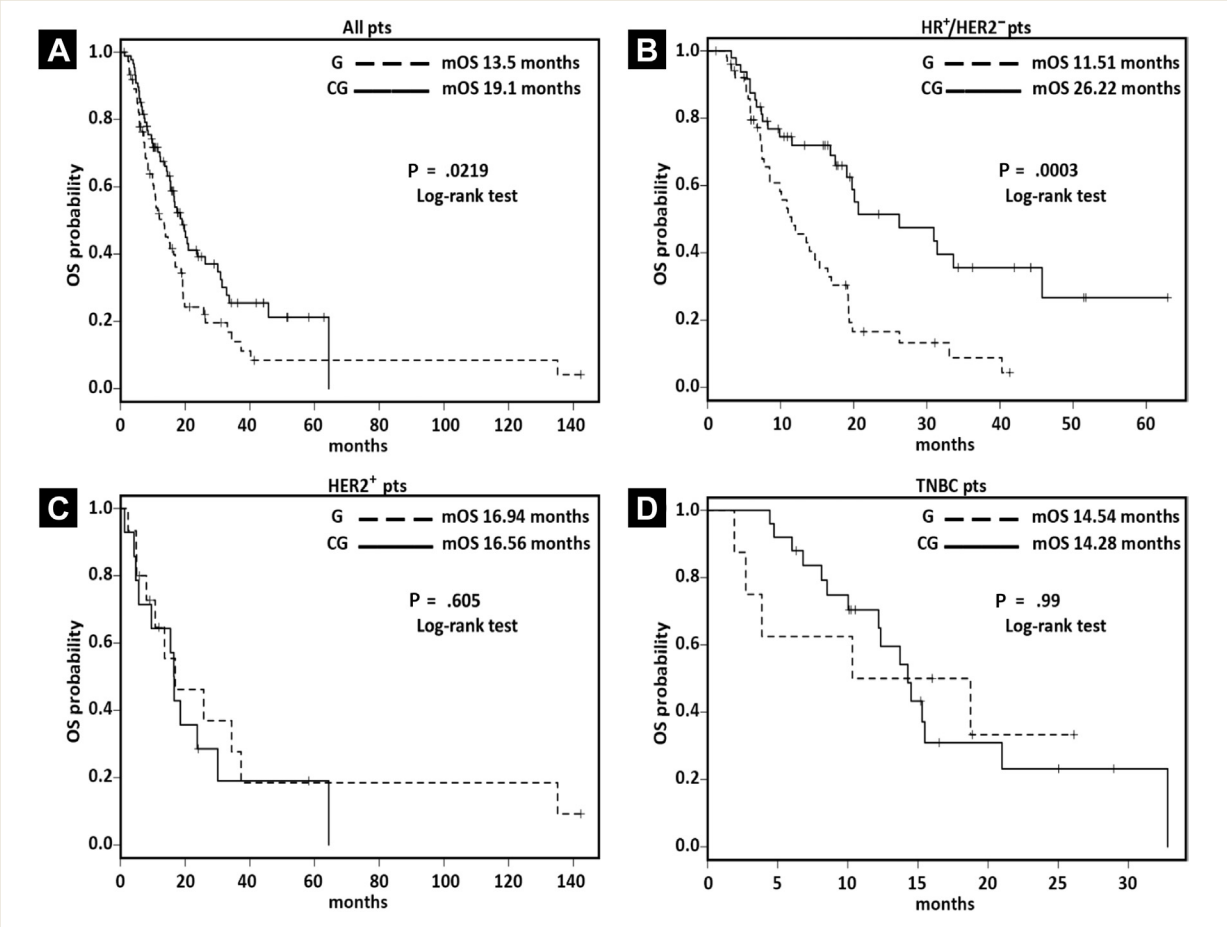
One hundred sixty-three consecutive mBC patients treated between April 2012 and February 2018 at our institution met the inclusion criteria. Of them, 75 received single-agent G, whereas 88 were treated with CG. All patients were evaluable for PFS, whereas only 1 patient was excluded from OS analysis because she was lost to follow-up after tumor progression during study treatment. Patient characteristics are described in Table 1. The median age was 58 (range, 32-80) years, and 82 patients (50.3%) had an ECOG PS of 0. One hundred one patients(62%) had HR^+ $HER2^-$ BC, 29 (17.8%) had $HER2^+$ BC, whereas the remaining 33 (20.2%) had TNBC. Among 29 patients with $HER2^+$ disease, 19 (65.5%) received trastuzumab in combination with G or CG.

Figure 1 Kaplan–Meier Curves of Progression-Free Survival in the (A) Overall Population and in (B) Patients With HR^+ $HER2^-$, (C) $HER2^+$, and (D) Triple-Negative Breast Cancer (TNBC). The "+" Symbol Indicates Patients Censored at the Time of Data Cutoff and Analysis



Abbreviations: C = carboplatin; G = gemcitabine; mPFS = median progression-free survival; pts = patients.

Figure 2 Kaplan–Meier Curves of Overall Survival (OS) in the (A) Overall Population and (B) in Patients With HR^+ $HER2^-$, (C) $HER2^+$, and (D) Triple-Negative Breast Cancer (TNBC). The "+" Symbol Indicates Patients Censored at the Time of Data Cutoff and Analysis



Abbreviations: C = carboplatin; G = gemcitabine; mOS = median overall survival; pts = patients.

There were no significant differences between G- and CG-treated patients in terms of age at treatment initiation ($P = .085$), ECOG PS ($P = .51$), number of metastatic sites ($P = .77$), presence of visceral metastases ($P = .59$), and previous exposure to anthracyclines ($P = .85$) or taxanes ($P = .73$). Patients in the CG cohort had received a lower number of previous ChT lines compared with patients treated with G ($P = .0092$); in particular, CG was the third ChT line (median, 3; range, 1-7), whereas single-agent G was the fourth-line (median, 4; range, 1- 10). Patients treated with CG were less likely to have HR^+ HER^- BC ($P = .0178$), whereas they were more likely to have been diagnosed with de novo metastatic disease ($P = .019$) and more frequently received maintenance treatment ($P = .0023$).

Treatment Efficacy

Patients in both treatment cohorts received a median number of 5 ChT cycles, with a range of 1 to 30 cycles in G- (average, 6.12) and 1 to 20 cycles in CG-treated (average, 6.22) patients. In 17 of 88 patients (19.3%) in the CG cohort, combination ChT was stopped after a variable number of cycles because of poor tolerability, and single-agent C (n = 2; 2.3%) or single-agent G (n = 15; 17%) were continued. At the time of data cutoff and analysis (May 30, 2018), 150 disease progressions and 107 death events had occurred. Activity/efficacy study end points are summarized in Table 2.

Median PFS was 4.38 months in the overall population, with no differences between G- and CG-treated patients (4.61 and 4.24 months, respectively; $P = .942$; Figure 1A) in patients with any disease biology or with HR^+ $HER2^-$ BC (median PFS [mPFS] of 4.38 and 3.66 months, respectively; $P = .936$), $HER2^+$ BC (mPFS of 4.61 and 5.43 months, respectively; $P = .572$), and TNBC (mPFS of 4.03 and 6.58 months, respectively; $P = .775$; Figure 1B-D).

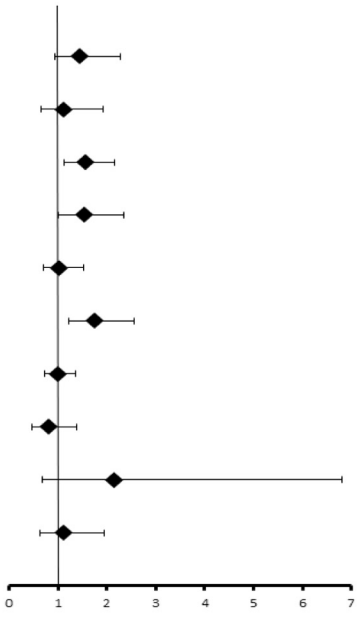
Median OS was 16.5 months in the overall population. Patients treated with CG had significantly longer OS compared with G-treated ones (19.1 and 13.5 months, respectively; $P = .0219$; Figure 2A). When considering tumor biology, CG was associated with better OS only in patients with HR^+ $HER2^-$ disease (26.22 and 11.51 months, respectively; $P = .0003$; (Figure 2B), but not in patients with $HER2^+$ BC (16.56 and 16.94 months, respectively;

Figure 3 (A) Univariable and (B) Multivariable Analysis of Patient Progression-Free Survival (PFS) According to Treatment Received and Other Meaningful Variables

A

Univariable analysis for PFS

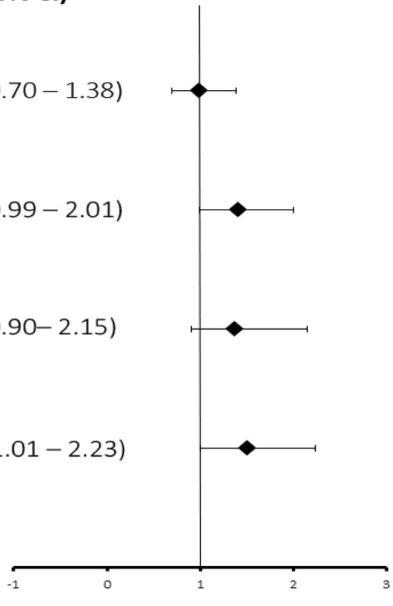
Variable	Patient n	Hazard Ratio (95% CI)	*P*
Biology subgroups:			
$^{-}HR^{+}$ *vs* $HER2^{+}$	130	1.45 (0.93 – 2.27)	.104
$^{-}TNBC$ *vs* $HER2^{+}$	62	1.11 (0.64 – 1.93)	.696
Line of treatment (>3 *vs* ≤3)	163	1.55 (1.12 – 2.15)	**.008**
Metastatic sites, n (>1 *vs* 1)	163	1.53 (1 – 2.34)	**.051**
Type of metastatic sites (visceral *vs* non visceral)	163	1.03 (0.69 – 1.52)	.897
Syncronous metastases (yes *vs* no)	163	1.76 (1.21 – 2.55)	**.003**
Type of treatment (CG *vs* G)	163	0.99 (0.71 – 1.37)	.942
Previous anthracyclines (yes *vs* no)	163	0.8 (0.46 – 1.39)	.428
Previous taxanes (yes *vs* no)	163	2.14 (0.67 – 6.8)	.198
Maintenance treatment (yes *vs* no)	163	1.11 (0.62 – 1.96)	.729



B

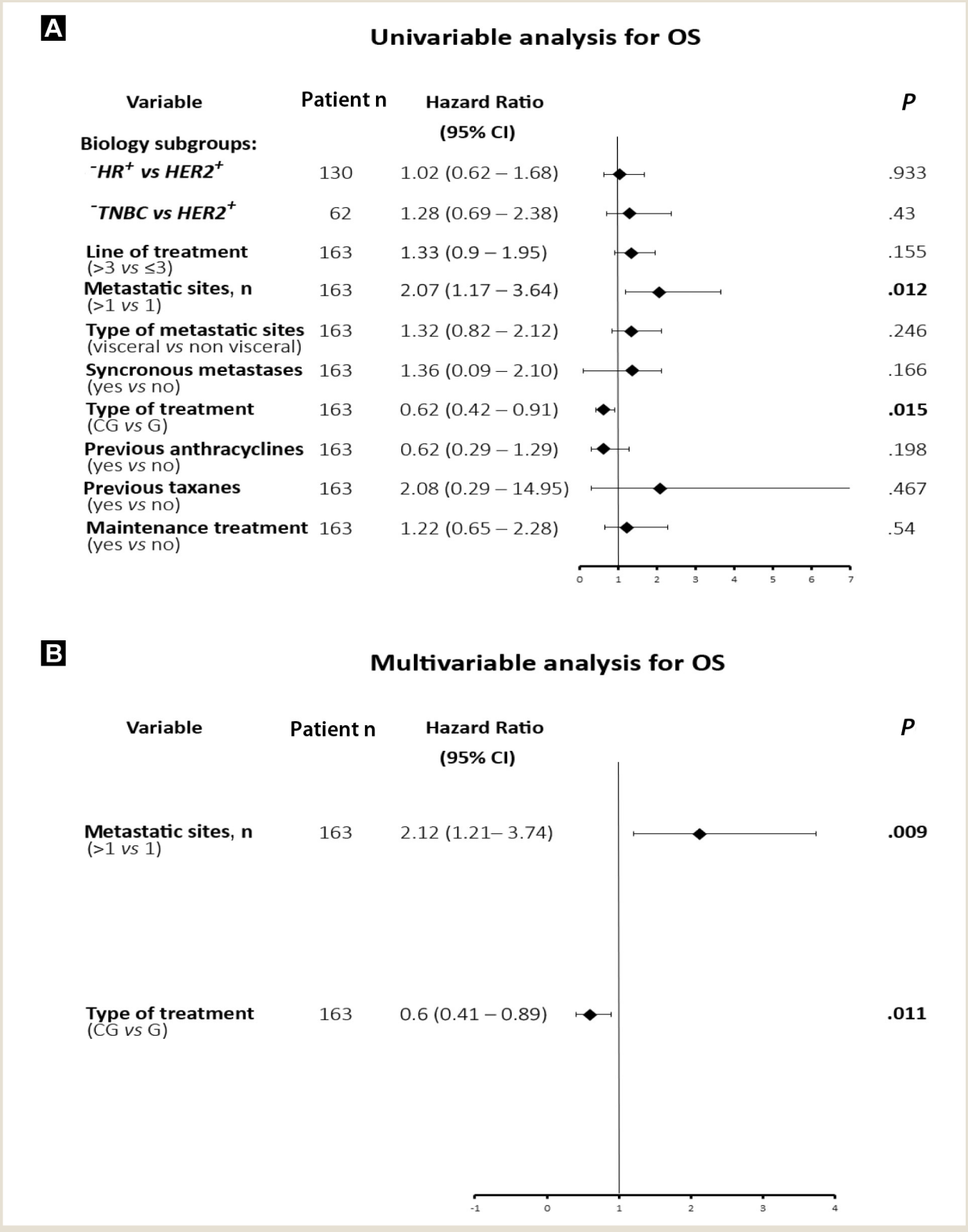
Multivariable analysis for PFS

Variable	Patient n	Hazard Ratio (95% CI)	*P*
Type of treatment (CG *vs* G)	163	0.98 (0.70 – 1.38)	.92
Line of treatment (>3 *vs* ≤3)	163	1.41 (0.99 – 2.01)	.057
Metastatic sites, n (>1 *vs* 1)	163	1.36 (0.90– 2.15)	.136
Syncronous metastases (yes *vs* no)	163	1.50 (1.01 – 2.23)	**.047**



Abbreviations: CG = carboplatin-gemcitabine combination; G = gemcitabine; HR = hormone receptor.

Figure 4 (A) Univariable and (B) Multivariable Analysis of Patient Overall Survival (OS) According to Treatment Received and Other Meaningful Variables



Abbreviations: CG = carboplatin-gemcitabine combination; G = gemcitabine; HR = hormone receptor.

Table 3 Rate of AEs That Occurred in Patients Treated With G or CG

AEs	G (n = 75)	CG (n = 88)	*P*
Any	69 (92)	86 (97.7)	.186
Neutropenia Any Grade	35 (46.7)	70 (79.5)	**<.0001**
Neutropenia Grade 3-4	5 (6.6)	30 (34)	**<.0001**
Anemia	50 (66.7)	75 (85.2)	**.0091**
Lymphopenia	31 (41.3)	34 (38.6)	.85
Thrombocytopenia Any Grade	14 (18.7)	25 (28.4)	.20
Thrombocytopenia Grade 3-4	2 (2.7)	4 (4.5)	.83
Nausea/Vomiting	9 (12)	22 (25)	.056
Constipation	4 (5.5)	8 (9)	.54
Diarrhea	3 (4)	4 (4.5)	1
Other GI Toxicities	18 (24)	18 (20)	.72
Other Toxicities	16 (21.3)	35 (39.7)	**.018**

Data are presented as n (%) except where otherwise noted. The *P* value of the proportion test for AEs is indicated in the right column of the table. *P* values are shown in bold when statistically significant.
Abbreviations: AE = adverse event; CG = carboplatin and gemcitabine combination; G = gemcitabine; GI = gastrointestinal.

$P = .605$; Figure 2C) or TNBC (14.28 and 14.54 months, respectively; $P = .99$; Figure 2D).

Among 155 patients evaluable for response, CG-treated patients had nonsignificantly better ORR compared with G-treated ones (18 patients [20.4%] vs. 8 patients [10.6%], respectively; $P = .089$).

Factors Independently Associated With Patient Prognosis

Variables associated with an increased risk of progression were: (1) having received >3 previous ChT lines ($P = .008$); (2) the number of metastatic sites (>1 vs. 1, $P = .051$); (3) having been diagnosed with de novo metastatic disease (ie, the presence of synchronous metastases; $P = .003$; Figure 3A). On the contrary, tumor biology (HR^+ $HER2^-$ vs. $HER2^+$, $P = .104$; TNBC vs. $HER2^+$, $P = .696$), previous exposure to anthracyclines ($P = .428$) or taxanes ($P = .198$), the type of metastatic spread (visceral vs. non-visceral; $P = .897$), and ChT regimen (G vs. CG; $P = .942$) were not associated with PFS (Figure 3A). In the multivariable model, the presence of de novo metastatic disease was the only variable to be still significantly associated with an increased risk of disease progression ($P = .047$; Figure 3B).

Regarding OS, a higher number of metastatic sites (>1 vs. 1) was associated with increased risk of death ($P = .012$), whereas CG treatment correlated with better survival ($P = .015$) (Figure 4A). Multivariable analysis confirmed the independent effect of these variables on patient OS (Figure 4B).

Treatment Safety and Tolerability

Treatment-related AEs are shown in Table 3. The incidence of any grade AEs was 92% with G and 97.7% with CG ($P = .186$), with hematologic AEs representing the most commonly reported ones (88% and 95.4%, respectively; $P = .144$). Grade3/4 neutropenia occurred significantly more frequently with the combination treatment (34%) than with single-agent G (6.6%; $P < .0001$), whereas febrile neutropenia was diagnosed in only 1 patient treated with CG. Granulocyte colony-stimulating factor was administered with a prophylactic or therapeutic intent to 29 (32.9%) patients treated with CG and to 11 (14.6%) patients who received single-agent G ($P = .012$). CG was also associated with higher incidence of any Grade anemia (85.2% with CG vs. 66.6% with G; $P = .0091$), whereas the rates of Grade 3/4 thrombocytopenia (4.5% vs. 2.7%; $P = .83$) and any Grade lymphopenia (38.6% vs. 41.3%; $P = .85$) were not significantly different. Regarding gastrointestinal AEs, nausea/vomiting were reported in 12% and 25% of patients in the C and CG groups, respectively ($P = .056$). The rate of treatment discontinuation because of AEs was significantly higher among CG-treated patients compared with those treated with G (10.2 vs. 0%; $P = .007$).

Exploratory Analyses

Patients treated with G were more likely to have previously received C than patients treated with CG (34 patients [45%] vs. 9 patients [10%]; $P < .0001$). When we evaluated patient PFS during the subsequent line of ChT, we found no significant differences between G- and CG-treated patients when the whole patient cohort was considered (3.57 vs. 3.26 months; $P = .111$). However, when limiting the analysis to patients with HR^+ $HER2^-$ disease, mPFS was significantly shorter among G-treated patients than among CG-treated ones (3.13 vs. 3.72 months; $P = .0171$; see Supplemental Figure 1 in the online version). Finally, when we measured OS from the diagnosis of metastatic disease to the date of patient death, we did not find significant differences between G- and CG-treated patients in the whole patient cohort (69 vs. 62.6 months; $P = .268$), nor among patients with HR^+ $HER2^-$ disease (70.7 vs. 78 months; $P = .605$; see Supplemental Figure 2 in the online version).

Systematic Review of the Literature

We searched in PubMed for prospective or retrospective studies reporting on the efficacy of G or CG in mBC patients. Collectively, we found 11 studies with G alone[15-25] and 9 studies with CG[30-39] (Table 4).[15-25,30-39] When used as single-agent ChT, G was given at different dosages (800-1250 mg/m^2) on days 1, 8, and 15 of every 28-day cycle; notably, the schedules used in each of these reports were less dense/intense than in our study. In reports testing the CG combination, ChT was administered on days 1 and 8 of every 21-day cycle; however, C dosage (AUC 2, 4, or 5) and schedule (day 1 or days 1 and 8 of every 21-day cycle), as well as G dosage (800-1250 mg/m^2) varied across individual studies. ORR was heterogeneous across different studies, and ranged between 0 and 42% with single-agent G and 28% to 69.2% with CG. TTP and OS were similarly variable, with 1.9 to 6.3 and 7.8 to 51.9 months, respectively, with G, and 4.5 to 7 and 7.72 to 28.8 months, respectively, with CG.

Discussion

Although single-agent G is considered a moderately effective chemotherapeutic agent in mBC treatment, it is frequently combined with C to increase tumor responses, especially in fit patients with metastatic TNBC (mTNBC). However, because a direct comparison between G and CG has never been performed, it is unclear whether CG provides PFS or OS benefit.

Table 4 Systematic Review of Published Prospective Studies That Assessed the Efficacy of G or CG in Patients With Metastatic Breast Cancer

Reference	Regimen	n/Resp Eval	HER2 Status, %	Treatment Setting (Patient n)	Median Cycles, n	ORR, %	TTP, Months	OS, Months
Carmichael et al[15]	G 800 mg/m^2 d 1, 8, 15 q28	44/40	NR	First-line (14) Second-line (19) Adjuvant (7)	2.0	25	NR	11.5
Possinger et al[16]	G 1000 mg/m^2 d 1, 8, 15 q28	42/42	NR	First-line (42)	3.9	14.3	NR	15.2
Schmid et al[17]	G 250 mg/m^2 (over 6 hours) d 1, 8, 15 q28	20/20	NR	First-line (4) Second-line (5) ≥ Third-line (11)	NR	25	6.3	51.9
Brodowicz et al[20]	G 1250 mg/m^2 d 1, 8, 15 q28	25/25	NR	Second-line (9) ≥ Third-line (16)	5.1	22	NR	8.1 Second-line: 12.6 Third-line: 7.5
Gerson et al[18]	G 1250 mg/m^2 d 1, 8, 15 q28	19/19	NR	First-line (2) Second-line (6) ≥ Third-line (11)	NR	42	NR	10.4
Spielmann et al[21]	G 1200 mg/m^2 d 1, 8, 15 q28	47/41	NR	Second-line (32) ≥ Third-line (15)	3	29	NR (8.1 for responders)	18.6
Smorenburg et al[22]	G 1200 mg/m^2 d 1, 8, 15 q28	23/20	NR	Second-line (3) ≥ Third-line (20)	NR	0	1.9	7.8
Valerio et al[23]	G 1000 mg/m^2 d 1, 8, 15 q28	26/22	NR	Second-line and ≥ third-line (26)	NR	23	NR	NR
Blackstein et al[19]	G 1200 mg/m^2 d 1, 8, 15 q28	39/35	NR	First-line (39)	4	37.1	5.1	21.1
Rha et al[25]	G 850 mg/m^2 d 1, 8, 15 q28	41/38	Positive (12) Negative (8) Unknown (21)	≥ Third-line (41)	4	20	4.5	11
Modi et al[24]	G 800 mg/m^2 d 1, 8, 15 q28	22/18	NR	Second-line (4) ≥ Third- line (18)	7.4 Infusions	17	NR	9.5
Latini et al[30]	G 1000 mg/m^2 d 1, 8 C AUC 5 d 1 q21	13/13	NR	NA	NA	69.2	NR	NR
Nasr et al[31]	G 1000 mg/m^2 d 1, 8 C AUC 5 d 1 q21	30/25	NR	Second-line (30)	NR	30	20.47 Weeks	Not reached
Silva et al[32]	G 1000 mg/m^2 d 1, 8 C AUC 5 d 1 q21	19/19	NR	Second-line and ≥ third-line (19) Pretreated with anthracyclines and taxanes (19)	4	21.5	NR	7.5
Catania et al[33]	G 1000 mg/m^2 d 1, 8 (G 1250 mg/m^2 d 1, 8 for first 4 patients) C AUC 4 d 1 q21	28/23	NR	Second-line (7) ≥ Third-line (21) Pretreated with anthracyclines and taxanes (11)	NR	21.7	NR	NR
Laessig et al[34]	G 1000 mg/m^2 d 1, 8 C AUC 4 d 1 q21	39/39	IHC scores = 0-1-2 (28) IHC score = 3 (10) Unknown IHC score = (3)	First-line (6) Second-line (14) ≥ Third-line (19)	5	30.8	5.3	13.2
Nagourney et al[35]	G 800 mg/m^2 d 1, 8 C AUC 2 d 1, 8 q21	15/13	Positive (4) Negative (11)	Second-line (15)	NR	53.3	4.5	28.8
Chan et al[36]	G 1000 mg/m^2 d 1, 8 C AUC 5 d 1 q21	41/38	Positive (8) Negative (12) Unknown (21)	First-line (5) Second-line (25) ≥ Third-line (11)	4	39	4.6	10.5
Nelli et al[37]	G 1000 mg/m^2 d 1, 8 C AUC 5 d 1 q21	42/40	Positive (14) Negative (28)	First-line (1) Second-line (29) ≥ Third-line (12)	NR	28	7	10.5

Table 4 Continued

Reference	Regimen	n/Resp Eval	HER2 Status, %	Treatment Setting (Patient n)	Median Cycles, n	ORR, %	TTP, Months	OS, Months
Zedan et al[38]	G 1000 mg/m^2 d 1, 8 C AUC 4 d 1 q21	50/50	0 (2) 1+ (1) 2 +(2) Unknown (45)	First- or second-line (47) ≥ Third-line (3)	6	60	5.73	7.72
Maisano et al[39]	G C	31/31	Negative (31)	≥ Second-line	NR	32	5.5	11

Abbreviations: AUC = area under the curve; C = carboplatin; d = day; G = gemcitabine; NA, not available; OS = overall survival; q21 = every 21 days; q28 = every 28 days; n/Resp Eval = number of patients evaluated for tumor response; TTP = time to progression.

In this study, we compared the antitumor efficacy and safety profiles of G and CG in 163 consecutive patients with mBC treated at our institution. We found a significantly greater incidence of severe hematologic AEs among CG-treated patients, with a trend toward greater ORR in the combination cohort and no PFS differences between the 2 groups, also after adjusting for relevant tumor- or patient-related variables. In our study, patients who received CG were less heavily pretreated, and therefore potentially more likely to benefit from the proposed ChT. The fact that CG was not associated with longer PFS even in a less pretreated population suggests the lack of a real advantage from adding C to G in unselected mBC patients. In the combination cohort, a higher rate of AE-related treatment discontinuations might have at least in part contributed to the lack of PFS advantage.

Results of our analyses are consistent with previously published studies, which associated combination ChT with higher response rates but also with increased toxicity, without providing a clear survival benefit to mBC patients.[14]

Quite unexpectedly, OS was higher in patients receiving CG, and in particular in the HR$^+$ HER2$^-$ subgroup. However, these results might reflect the fact that G-treated patients had received a higher number of previous ChT lines, and were more likely to have chemoresistant disease and fewer available treatment options. This hypothesis is supported by the following facts: (1) more G-treated patients had previously received C; (2) in patients with HR$^+$ HER2$^-$ disease, the PFS during the subsequent treatment line was significantly longer among CG-treated patients, probably reflecting the availability of more treatment options; and (3) when we analyzed OS starting from the first documentation of metastatic disease, we found no differences between G- and CG-treated patients.

Collectively considered, our findings suggest that the additional use of C with G does not improve clinical outcomes, whereas it is clearly associated with significantly higher incidence of Grade 3/4 neutropenia and a higher rate of treatment discontinuation. Although the potential role of combination ChT in first and second treatment lines remains a debated topic, results of our study should discourage clinicians from indiscriminately prescribing the CG combination to unselected mBC patients, especially in more advanced treatment lines. Of course, this does not exclude that selected patient populations could benefit from CG. In this perspective, it will be essential to find predictive factors that are able to identify patients who can actually benefit from platinum-containing combinations. For instance, a recent study has shown that first-line C monotherapy is associated with higher ORR and better PFS compared with docetaxel monotherapy (68% vs. 33% and 6.8 vs. 4.4 months, respectively) in patients with mTNBC and germline mutations in breast-related cancer antigen (*BRCA) 1/2* genes.[40] In addition, we have recently shown that higher neutrophil to lymphocyte ratio and platelet to lymphocyte ratio predict poorer benefit from platinum-based ChT in patients with mTNBC but not HR$^+$ HER2$^-$ mBC.[41]

On the basis of the available evidence from randomized trials, patients with *BRCA1/2*-mutated mTNBC bearing alterations in the homologous recombination pathway could benefit from first-line platinum-based ChT.[40] The CG combination could be also useful for patients in whom fast tumor shrinkage is needed (eg, for the presence of massive visceral involvement or visceral crisis in patients with mTNBC). Among platinum-based doublets, the combination of cisplatin and G has also shown an acceptable tolerability profile and good antitumor activity, with a relative lack of cross-resistance with other drug combinations.[42-45] Although the best schedule and dosages of individual drugs are not clearly understood, the following schedules have been shown to be feasible even in populations of previously pretreated mBC patients: cisplatin 75 mg/m^2 on day 1 with G 1250 mg/m^2 on days 1 and 8 every 3 weeks; cisplatin 50 mg/m^2 with G 2500 mg/m^2 every 2 weeks; cisplatin 30 mg/m^2 with G 1000 mg/m^2 on days 1 and 8 every 3 weeks; and cisplatin 30 mg/m^2 with G 1000 mg/m^2 on days 1, 8, and 15 every 4 weeks.[42-45]

Independently from the issue of ChT combinations, the opportunity of introducing platinum salts at some point during the course of mBC treatment remains a debated topic in the oncology community.[46] Although previous analyses suggest a possible survival advantage, this evidence is limited by poor patient selection. Moreover, even among patients with germline/somatic inactivating mutations of *BRCA1/BRCA2* genes, it is not clear if platinum-based combinations, and, which specific combination (eg, with a taxane or G), improve patient survival.[47] Indeed, Tutt et al[40] tested C versus docetaxel monotherapy, whereas the efficacy of platinum-based combinations (including CG) remains unclear even in this selected population of patients. Moreover, a recent study has shown the superiority, in terms of PFS, of C with nab-paclitaxel over CG or G with nab-paclitaxel in the first treatment of mTNBC.[48] These results show that, even among mTNBC patients, the CG combination could not necessarily be the most effective platinum-based combination.

Strengths of this study consist of homogeneous recording of clinical data and ChT schedules at our institution, as well as the relatively short time window (years 2012-2018), which minimizes the effect of major changes in mBC management resulting from the introduction of new drugs. Weaknesses consist of the retrospective

design of the study, as well as the limited number and heterogeneity of patients included.

Conclusion

Single-agent G, administered at a dosage of 800 mg/m^2 on days 1 and 8 of every 3-week cycle, represents an acceptably safe and effective ChT option for patients with heavily pretreated mBC. Additional use of C with G is associated with higher hematologic toxicities but not with better PFS. Prospective studies are required to identify subgroups of mBC patients who could benefit from combining C with specific cytotoxic agents, such as G and taxanes.

Clinical Practice Points

- G and CG are frequently used in the treatment of advanced BC, especially in more advanced therapy lines. While CG may be more effective than single-agent G in patients with advanced TNBC, no studies have compared G and CG in specific BC populations. In this study, we retrospectively evaluated the safety, activity, and clinical efficacy of G and CG in a heterogeneous population of patients with advanced BC.
- We found that CG is associated with a trend toward better ORR compared to single-agent G. These finding are consistent with previously reported prospective studies demonstrating that several combination chemotherapy regimens are more active than single-agent regimens. Despite this trend suggesting higher antitumor activity, CG was associated with a significantly higher incidence of AEs, in particular hematologic ones, without any evidence of higher efficacy (PFS) in any biological subgroup (HR^+HER2^-, $HER2^+$, TNBC).
- On the basis of these findings, as well as those of previously published studies, clinicians should be aware that there is no convincing evidence for indiscriminately prescribing CG to unselected populations of patients with advanced BC.
- While prospective studies are needed to test the hypothesis that CG may benefit specific patient subgroups—for instance, patients with *BRCA1/2*-mutated TNBC—single-agent G remains a well-tolerated, moderately effective treatment in more advanced treatment lines as well.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2018.12.004.

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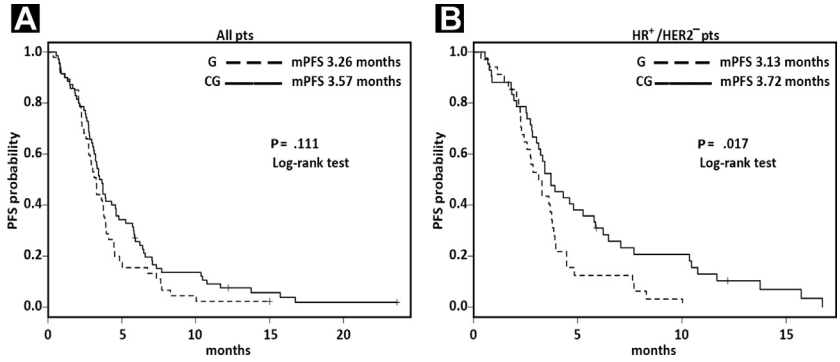
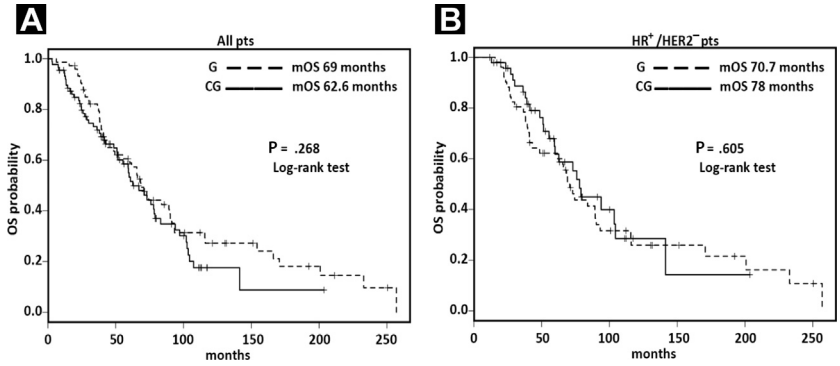
Supplemental Figure 1 Kaplan–Meier Curves of Progression-Free Survival (PFS) During the Subsequent Line of Chemotherapy in the (A) Overall Population and (B) Within the Subgroup of Patients With HR^+ $HER2^-$ Biology. The "+" Symbol Indicates Patients Censored at the Time of Data Cutoff and Analysis



Abbreviations: C = carboplatin; G = gemcitabine; mPFS = median progression-free survival; pts = patients.

Supplemental Figure 2 Kaplan–Meier Curves of Overall Survival (OS) From Time of Diagnosis of Metastatic Disease to the Date of Patient Death From Any Cause in the (A) Overall Population and (B) Within the Subgroup of Patients With HR^+ $HER2^-$ Biology



Abbreviations: C = carboplatin; G = gemcitabine; mOS = median overall survival; pts = patients.