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Progestin as an alternative treatment option for multi-treated recurrent triple-negative breast cancer

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Summary

OBJECTIVE: Patients with recurrent triple-negative breast cancer (TNBC) currently have no established treatment option other than chemotherapy. However, long-term chemotherapy is often difficult due to adverse effects. A previous study documented a 10%–30% response rate of progestins in oestrogen receptor–negative breast cancer. The aim of this study was to investigate the effect of medroxyprogesterone/megestrol acetate (MPA/MA) in patients with recurrent TNBC.

METHODS: This retrospective observational analysis included 51 patients with recurrent TNBC; 17 were treated with MPA/MA and 34 underwent chemotherapy. The two groups were matched at a 1:2 ratio according to age, metastatic sites, and salvage treatment lines. Efficacy was compared using the χ^2 and rank-sum tests. Progression-free survival (PFS) was calculated using the Kaplan–Meier method, and the two groups were compared using the log-rank test.

RESULTS: The two groups were well balanced in terms of age, disease-free survival, number of metastases, and salvage therapy lines. Clinical benefit rates in the MPA/MA and chemotherapy groups were 52.94% and 73.53%, respectively (χ^2 test, $p = 0.208$), and median PFS was comparable between groups (log-rank test, $p = 0.135$). Median PFS of 1^{st}–6^{th}-line salvage treatments was shorter in the MPA/MA group than in the chemotherapy group (log-rank test, $p = 0.036$), but median PFS of $\geq 7^{th}$-line salvage treatments was comparable (log-rank test, $p = 0.139$). Eight patients discontinued chemotherapy due to adverse effects, and one patient withdrew from MPA treatment because of weight gain.

CONCLUSIONS: Progestins (MPA/MA) are an alternative treatment option for multi-treated recurrent TNBC.

Key words: *recurrent breast cancer; triple-negative breast cancer; medroxyprogesterone acetate; megestrol acetate*

Introduction

Tumours without oestrogen receptor (ER), progesterone receptor (PgR), or human epidermal growth factor receptor 2 (HER2) expression are referred to as triple-negative breast cancer (TNBC), representing about 15% of all breast cancers [1–4]. TNBC has an aggressive clinical phenotype with early brain and other distant metastases and a poor prognosis [5–9]. This form of cancer constitutes an important clinical challenge because it is not likely to respond to anti-oestrogen therapy or HER2 antagonists. At present, patients with recurrent TNBC currently have no established treatment option other than chemotherapy [10]. However, the long-term use of chemotherapeutic agents is difficult because of side effects, especially in multi-treated patients. Effective and sustainable therapeutic avenues are greatly needed, as the interruption of treatment may lead to rapid progression.

Endocrine manipulations are generally well tolerated. Selective estrogen response modulators and aromatase inhibitors (AIs) are currently the most commonly used endocrine agents, but such drugs mainly target hormone receptor–positive breast cancers [11, 12]. The progestins megestrol acetate (MA) and medroxyprogesterone acetate (MPA) were used frequently until the early 1990's as a second-line hormonal therapy for metastatic breast cancer [13]. A previous study showed that MPA and MA achieved comparable median progression-free survival (PFS) [14], and the two agents were more effective in patients with hormone receptor–positive breast cancer than in those with hormone receptor–negative breast cancer. MPA and MA have shown 10%–30% response rates in patients with ER-negative breast cancer [15, 16]. In the 1990's, our team reported comparable response rates in patients with ER-negative and ER-positive breast cancer who were treated with progestins [15]. Although the use of progestins declined following the advent of selective estrogen response modulators and AIs, practitioners have recently shown renewed interest in the use of alternative hormonal treatments when conventional therapies fail [16, 17]. Furthermore, MPA/MA is also frequently used in patients with advanced malignancies to improve quality of life [18], especially with respect to appetite [19]; most research on this topic has been published in Chinese.

As TNBC is a relatively newly defined subgroup of breast cancer, older clinical trials did not differentiate breast can-

cer types in terms of ER, PgR, and HER2 status. While research continues to identify potential new targets based on phenotypic and molecular characteristics of these tumours [20–25], formerly popular agents whose use has declined may remain effective in triple-negative disease. Whether a single progestin is a suitable therapy for multi-treated TNBC should be examined.

To investigate the effect of MPA/MA in patients with recurrent TNBC, we conducted a retrospective observational study to review the outcomes of a sample of patients treated with MPA/MA and chemotherapy at our hospital between 2002 and 2011.

Methods

The Ethics Committee and Review Board of the Affiliated Hospital of the Academy of Military Medical Sciences approved this study.

Patient selection

In this single-institution retrospective study, we used data from a representative sample of 2,475 patients with breast cancer who had been hospitalised between 1 January 2002 and 31 December 2011. The following information was collected from original medical records: patient age and sex, dates of primary invasive breast cancer and metastasis diagnoses, initial tumour stage, metastasis sites, adjuvant therapy, lines and regimens of salvage therapy, PFS, and adverse events. The inclusion criteria were primary breast cancer diagnosis; proven metastatic disease; and ER, PgR and HER2 testing in primary and metastatic tumours. The exclusion criteria were prior salvage therapy (including chemotherapy, hormone therapy, and target therapy) within 3 weeks, and prior treatment using the same regimen. Patient characteristics are presented in table 1.

In this cohort, 252 patients had been diagnosed with primary TNBC, and metastases were diagnosed in 190 of these patients. Triple-negative tumours were diagnosed at primary and metastatic sites in 118 patients. Only 17 patients with TNBC who received progestin (MPA/MA) treatment were included in our database. To create a statistical model in which patients in the MPA/MA and chemotherapy groups were matched at a 1:2 ratio according to age, metastatic sites, and lines of salvage treatment, we selected 34/101 patients in the database who had undergone chemotherapy for inclusion in this study. We believe that the use of this model is more effective than analysis using an unselected model. A flow chart of the cohort is presented in figure 1.

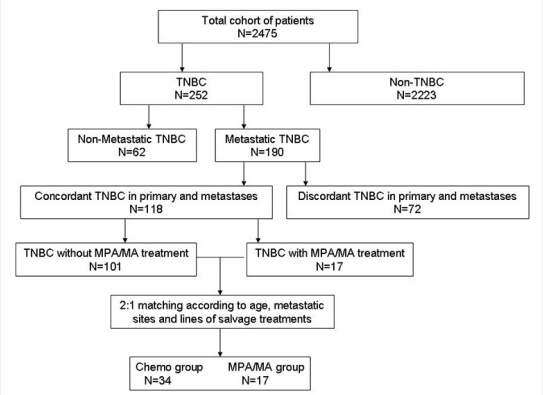


Figure 1

Flow chart of patient selection.
TNBC, triple-negative breast cancer; MPA/MA, medroxyprogesterone acetate/megestrol acetate.

Pathology

Primary and metastatic ER, PgR, and HER2 data were collected from pathology reports. ER and PgR status were evaluated by immunohistochemistry (IHC) and classified as positive (≥10% cells immunostained) or negative [26]. HER2 status was evaluated by IHC and/or fluorescence *in situ* hybridisation (FISH) [27]. According to the Hercep Test criteria, the immunoreaction of specimens was scored as 3+, 2+, 1+ or 0 [28]. Tumours scored as 3+ by IHC or FISH (+) were considered HER2 positive, and those scored as 0/1+ by IHC or FISH (–) were designated as HER2 negative.

Treatment

Each patient in the MPA/MA group was treated with a single progestin agent: 500 mg oral MPA (10/17, 58.82%) or 160 mg oral MA (7/17, 41.18%) daily. In the chemotherapy group, 21 patients (61.76%) were treated with single-agent chemotherapy, and 13 patients (38.24%) underwent combined chemotherapy. Chemotherapy regimens (table 2) included anthracyclines, taxanes, platinum, gemcitabine, vinorelbine, capecitabine, or etoposide; regimens varied among patients because they were selected according to each patient's prior therapy and general condition. The doses of chemotherapeutic agents and treatment intervals were adjusted according to each patient's physical condition and adverse effects.

Treatment of patients in both groups continued until disease progression or an unacceptable adverse effect was noted. The therapeutic effect, time to progression, and curative and side effects were recorded. Adverse effects were assessed using the Common Terminology Criteria for Adverse Events, version 3.0 [29]. PFS was defined as the time from the date of administration to the date of disease progression. The Response Evaluation Criteria in Solid Tumours (RECIST; ver. 1.0) were used to classify disease status as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) [30]. Assessable lesions were deemed to have shown clinical benefit (CB) when objective responses were classified as a CR or PR, or when SD persisted ≥6 months, in accordance with the Union for International Cancer Control criteria [31, 32]. Disease control status was defined as the "best status to date," specifically whether patients showed CR, PR, or SD [33].

Statistical analysis

Data were analysed using SAS statistical software (version 9.2; SAS Institute, Cary, NC, USA). Patient characteristics, CB rates, and disease control rates were compared between groups using the χ^2 test. The rank-sum test was used to compare therapeutic effects between groups. PFS was es-

timated using to the Kaplan–Meier product limit method, and groups were compared with the log-rank test.

Results

The two groups were well balanced in terms of patient age, disease-free survival, metastasis, number of metastases, and lines of salvage therapy (table 1). Mean patient ages in the MPA/MA (n = 17) and chemotherapy (n = 34) groups were 53.60 and 52.10 years, respectively. In the entire study sample, 70.59% of patients received 1st–6th-line therapy for metastatic disease. All patients in the MPA/MA group were treated with a single agent, and 38.23% (13/34) of patients in the chemotherapy group underwent combination chemotherapy.

Therapeutic effect

All patients had target lesions, allowing the use of RECIST to evaluate objective responses. Therapeutic effects are presented in table 3. One case of CR and three cases of PR were observed in the chemotherapy group, but no such cases were documented in the MPA/MA group. More SD cases and fewer PD cases occurred in the chemotherapy group than in the MPA/MA group, but overall efficacy did not differ significantly between groups (rank-sum test, $p = 0.076$). Disease control rates were 52.94% (9/17) in the MPA/MA group and 73.53% (25/34) in the chemotherapy group (χ^2 test, $p = 0.208$). CB rates (CR + PR + SD ≥ 6 months) showed no significant difference between the MPA/MA and chemotherapy groups (11.76% *vs*. 29.41%; χ^2 test, $p = 0.263$). More than 35% of patients in each group showed at least 3 months of CB (CR + PR + SD ≥3 months). Patients in the MPA/MA group showed a marked response to treatment that continued for more than 7 months.

Progression-free survival

Median PFS was comparable in the MPA/MA and chemotherapy groups {2 [95% confidence interval (CI), 1–4] *vs*. 2.5 [95% CI, 2–5] months; log-rank test, $p = 0.135$}. Median PFS of 1st–6th-line salvage treatments was shorter in the MPA/MA group than in the chemotherapy group [2 (95% CI, 1–4) *vs*. 5 (95% CI, 2–7) months; log-rank test, $p = 0.036$], but median PFS of ≥7th-line salvage treatments was

Table 1: Patient characteristics.

	MPA/MA group (n = 17)	Chemotherapy group (n = 34)	t or χ^2	p
Age, years (mean ± standard deviation)	53.60 ± 11.00	52.10 ± 12.30	1.010	0.319
Median disease-free survival, months [median (range)]	17.50 (10, 40)	27.00 (19, 41)	0.821	0.365
Metastases, % (n)				
Viscera	82.35 (14/17)	73.52 (25/34)	0.490	0.728
Bone	29.41 (5/17)	44.12 (15/34)	1.028	0.373
Brain	5.88 (1/17)	5.88 (2/34)	0.000	1.000
Lymph node/soft tissue	70.59 (12/17)	64.71 (22/34)	0.177	0.760
Number of metastases, % (n)				
1–2	52.94 (9/17)	73.52 (25/34)	2.162	0.208
≥3	47.06 (8/17)	26.47 (9/34)	2.162	0.208
Lines of salvage therapy, % (n)				
1–3	23.53 (4/17)	26.47 (9/34)	0.052	1.000
4–6	47.06 (8/17)	44.12 (15/34)	0.040	1.000
7–9	23.59 (4/17)	26.47 (9/34)	0.052	1.000
≥10	5.88 (1/17)	2.94 (1/34)	0.260	1.000

MPA/MA, medroxyprogesterone acetate/megestrol acetate.

Table 2: Salvage therapy regimens.

	MPA/MA group (n = 17)	Chemotherapy group (n = 34)
Salvage therapy regimen, % (n)		
Megestrol acetate	41.18 (7/17)	
Medroxyprogesterone	58.82 (10/17)	
Containing anthracyclines		8.82 (3/34)
Containing taxanes		26.47 (9/34)
Containing platinum		20.59 (7/34)
Containing gemcitabine		14.71 (5/34)
Containing vinorelbine		17.65 (6/34)
Containing capecitabine		14.71 (5/34)
Containing etoposide		17.65 (6/34)
1–6 lines, % (n)		
Single-agent therapy	100 (12/12)	58.33 (14/24)
Combination therapy		41.67 (10/24)
≥7 lines, % (n)		
Single-agent therapy	100 (5/5)	70.00 (7/10)
Combination therapy		30.00 (3/10)

MPA/MA, medroxyprogesterone acetate/megestrol acetate.

comparable between groups [2 (95% CI, 1–2) *vs*. 2 (95% CI, 1–6) months; log-rank test, $p = 0.139$]. Median PFS was comparable between patients treated with MPA ($n = 7$) and those treated with MA [$n = 10$; 2 (95% CI, 2–4) *vs*. 1.5 (95% CI, 1–4) months; log-rank test, $p = 0.921$]. Survival curves are presented in figure 2.

Adverse effects

No serious side effect occurred in the MPA/MA group; moderate side effects included body weight gain, hyperglycaemia, vaginal bleeding, and blurred vision. One patient withdrew from MPA treatment because of weight gain. Eight patients (23.52%) in the chemotherapy group withdrew because of adverse effects. The most frequent grade 3 or 4 adverse events in the chemotherapy group were neutropenia, leucopenia, thrombocytopenia, anaemia, fatigue or asthenia, and increased alanine aminotransferase level. Adverse effects and withdrawal data are presented in table 4.

Discussion

The results of this retrospective observational study demonstrate that MPA/MA has a comparable CB but lower toxicity than chemotherapy for patients with multi-treated (>7th-line salvage therapy) recurrent TNBC. These findings will be useful for clinicians in the management of patients with recurrent TNBC. Because this disease is incurable, sustainable systemic therapy is needed to prolong survival. The long-term use of chemotherapeutic agents is difficult due to side effects, and treatment interruption may lead to rapid progression. MPA/MA may have relevant clinical implications for patients with recurrent TNBC, especially for multi-treated patients with poor general conditions.

TNBC is currently the subject of active research, and several novel classes of drug are under investigation or clinical development [20–25]. A previous study showed that these novel agents, such as histone deacetylase inhibitor [25], may have a curative effect on breast cancer, but none are currently routinely used in clinical practice. Several studies have shown that MPA/MA has a curative effect on breast cancer, even on ER-negative tumours [15, 16]. A literature search found that no previous study examined the treatment of recurrent TNBC with a single progestin agent (MPA or MA); this study is thus, the first to do so.

A previous study conducted in our hospital showed that MPA/MA treatment achieved a comparable response rate in patients with hormone receptor–positive and –negative breast cancer [15]. Although MPA was designed to bind with high affinity to the PgR, androgenic side effects observed in women taking MPA suggested that the androgen receptor (AR) may contribute to its activity *in vivo*. This hypothesis is supported by the high binding affinity of MPA to the AR [34], and clinical studies have shown that

Table 3: Therapeutic effects.

	MPA/MA group ($n = 17$)	Chemotherapy group ($n = 34$)	χ^2	p
Therapeutic effect, % (n)				
CR	0	2.94 (1/34)	3.157	0.076
PR	0	8.82 (3/34)		
SD	52.94 (9/17)	61.76 (21/34)		
PD	47.06 (8/17)	26.47 (9/34)		
Clinical control rate (CR + PR + SD)	52.94 (9/17)	73.53 (25/34)	2.162	0.208
CR + PR + SD ≥6 months	11.76 (2/17)	29.41 (10/34)	1.962	0.293
CR + PR + SD ≥3 months	35.29 (6/17)	41.18 (14/34)	0.165	0.767
CR + PR + SD ≥4 months	29.41 (5/17)	32.35 (11/34)	0.046	1.000
CR + PR + SD ≥5 months	21.43 (3/17)	32.35 (11/34)	1.231	0.334

CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; MPA/MA: medroxyprogesterone acetate/megestrol acetate.

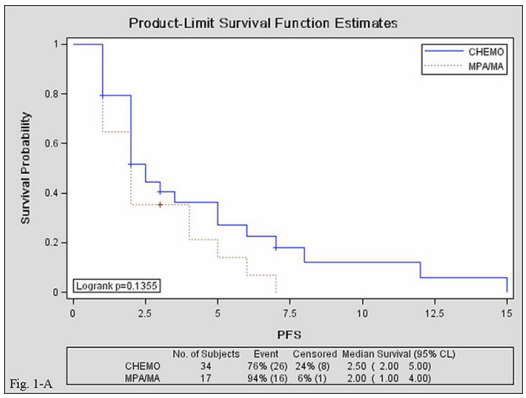
Table 4: Adverse effects and withdrawal from treatment.

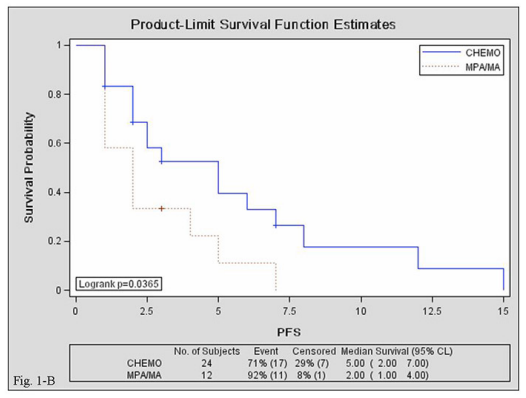
	MPA/MA group ($n = 17$)	Chemotherapy group ($n = 34$)
Adverse effects,* % (n)		
Grade 3–4 haematological toxicity		
Neutropenia	0	35.29 (12/34)
Leucopenia	0	44.12 (15/34)
Thrombocytopenia	0	5.88 (2/34)
Anaemia	0	14.71 (5/34)
Grade 3–4 non-haematological toxicity		
Fatigue or asthenia	0	55.89 (19/34)
Increased alanine aminotransferase level	5.88 (1/17)	47.06 (16/34)
Body weight gain	47.06 (8/17)	0
Hyperglycaemia	17.65 (3/17)	11.76 (4/34)
Vaginal bleeding	47.06 (8/17)	0
Blurred vision	5.88 (1/17)	5.88 (2/34)
Hand–foot syndrome	0	5.88 (2/34)
Withdrawal, % (n)	5.88 (1/17)	23.53 (8/34)

*Assessed using the Common Terminology Criteria for Adverse Events, version 3.0
MPA/MA, medroxyprogesterone acetate/megestrol acetate.

the response of breast tumours to high-dose MPA therapy is dependent on the expression of AR, but not ER or PgR [35, 36]. AR expression has been observed in about 50% of patients with TNBC [37], and may explain the efficacy of MPA/MA treatment in these patients.

This study had several limitations. First, the study was retrospective. Second, because selective oestrogen response modulators and AIs are more effective than progestin in patients with hormone receptor–positive breast cancer, the use of progestins has declined, so our patient sample was small and the results of this study are not generalisable to larger populations. Third, the statistical approach used in this study, including the matching of patients at a 1:2 ratio, is typically employed in randomised trials rather than in retrospective observational studies. However, only 17 patients with TNBC who received progestin treatment were included in our database, and the chemotherapy group was also selected from a very small cohort (34/101). Considering that patients were matched according to age, metastatic sites, and lines of salvage treatment, we believe that the use of a 1:2-matched statistical model was more effective than an unselected model.





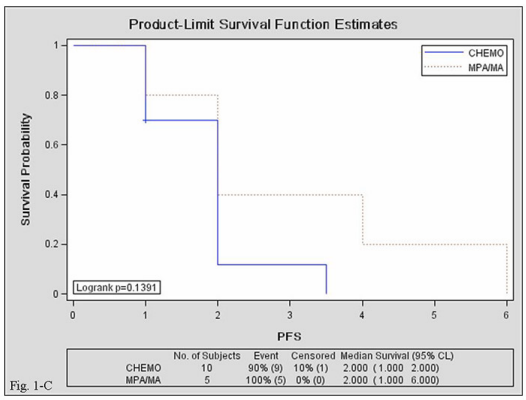


Figure 2

Kaplan–Meier curves for progression-free survival in the MPA/MA and chemotherapy groups. A: overall; B: 1–6 lines of salvage therapy; C: ≥7 lines of salvage therapy.

CHEMO, chemotherapy group; MPA/MA, medroxyprogesterone acetate/megestrol acetate group; PFS, progression-free survival; CI, confidence interval.

Conclusions

Our data provide clinical evidence that MPA/MA may be an alternative treatment for patients with recurrent TNBC, especially for multi-treated patients with poor physical conditions. However, our study was observational and the sample was small. Further studies with larger datasets and prospective research are needed to provide confirmatory evidence for or against the feasibility of MPA/MA treatment for recurrent TNBC.

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Figures (large format)

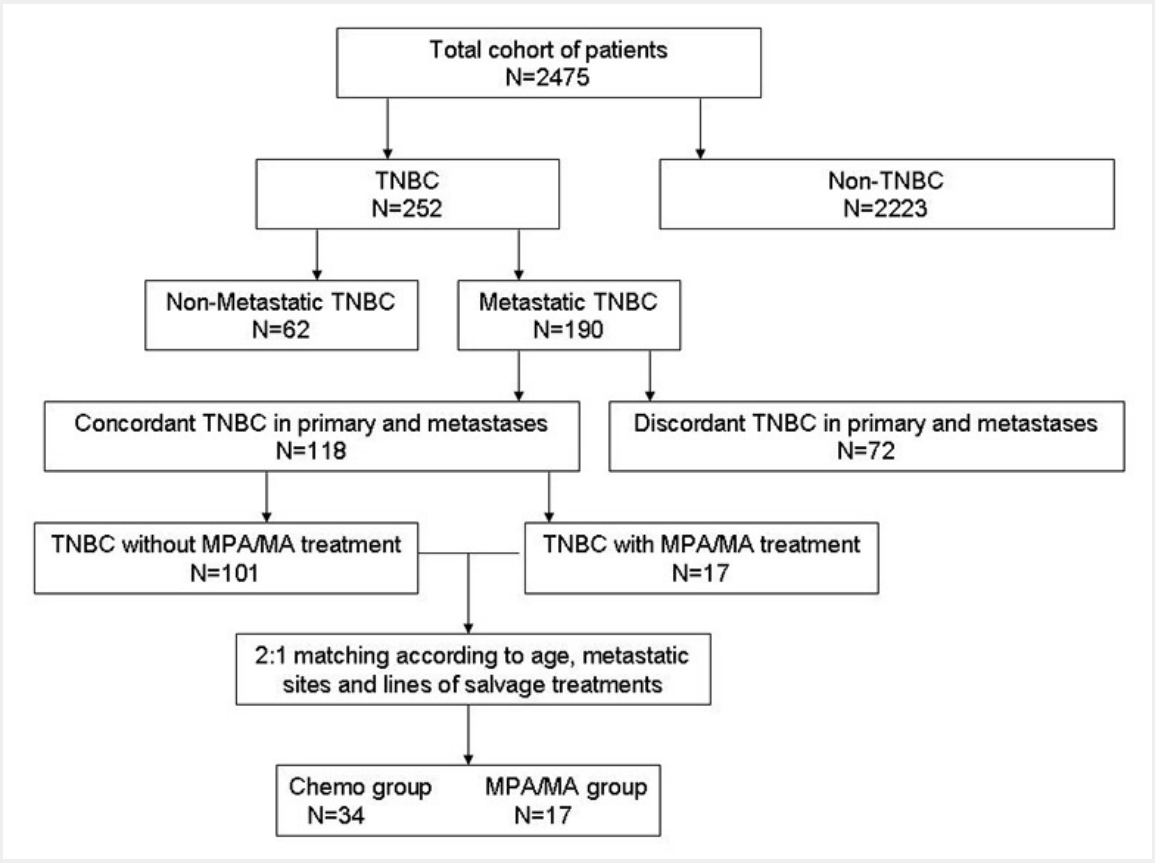
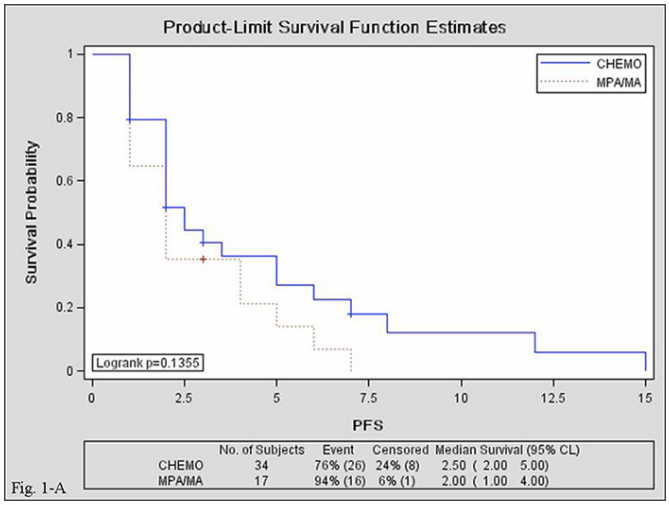
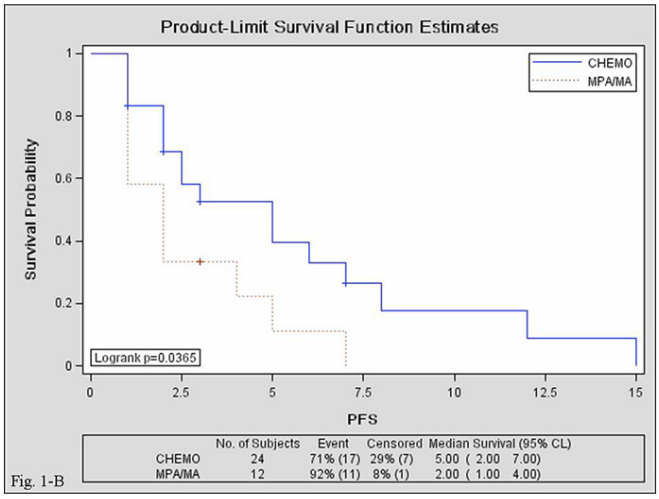


Figure 1

Flow chart of patient selection.
TNBC, triple-negative breast cancer; MPA/MA, medroxyprogesterone acetate/megestrol acetate.





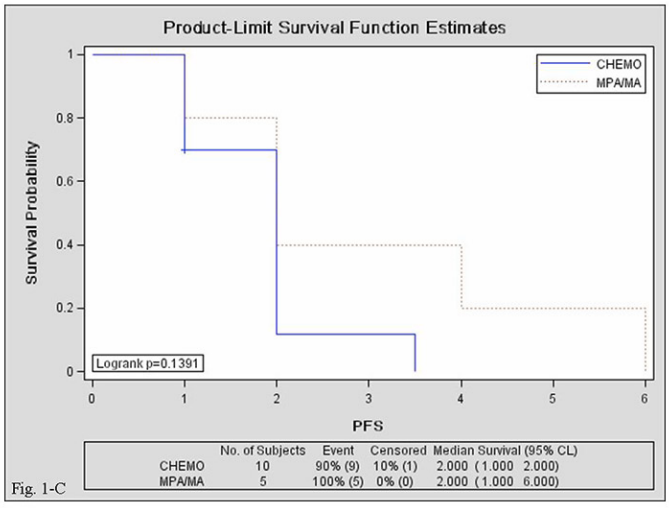


Figure 2

Kaplan–Meier curves for progression-free survival in the MPA/MA and chemotherapy groups. A, overall; B, 1–6 lines of salvage therapy; C, ≥7 lines of salvage therapy.

CHEMO, chemotherapy group; MPA/MA, medroxyprogesterone acetate/megestrol acetate group; PFS, progression-free survival; CI, confidence interval.