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Side Effects of Standard Adjuvant and Neoadjuvant Chemotherapy Regimens According to Age Groups in Primary Breast Cancer

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Summary

Background: Elderly breast cancer patients are underrepresented in clinical trials and this leads to a lack of knowledge regarding the tolerance and side effects of modern chemotherapy regimens, especially in dose-dense (dd) or dose-intensified combination. **Patients and Methods:** In this analysis, data from 4 German, randomized (neo-)adjuvant trials, including anthracycline-based chemotherapy, were evaluated for toxicity, compliance and feasibility. Patients were grouped according to age. **Results:** Of the 4,775 patients, 73.6% were < 60 years, 15.8% were 60–64 years and 10.6% were > 64 years. The patients' compliance decreased with increasing age, the rate of therapy discontinuations was 10.3%; 16.0% were > 64 years old ($p < 0.001$). The rate of dose reductions also increased with increasing age in the docetaxel/doxorubicin/cyclophosphamide (TAC) (p overall = 0.02) and 5-fluorouracil/epirubicin-cyclophosphamide ($FE_{120}C$) (p overall < 0.001) treatment groups. Neutropenia grade 3 + 4 in patients of > 64 years was 77% in $FE_{120}C$- compared to 55% in TAC-treated patients (with primary granulocyte colony-stimulating factors (G-CSFs)). The incidence of febrile neutropenia (FN) was lowest in the regimens without additional taxanes. FN in patients aged > 64 years was lower in the $FE_{120}C$- than in TAC- and dd-doxorubicin/docetaxel-treated groups. **Conclusion:** The range and intensity of toxicity increased with age. Neutropenia did not increase significantly in the dd groups; the highest rate was seen in $FE_{120}C$-treated patients. $FE_{120}C$ without G-CSFs is not an option in patients older than 64 years.

Zusammenfassung

Hintergrund: Ältere Patientinnen mit Brustkrebs sind in klinischen Studien unterrepräsentiert, was zu einem Kenntnismangel in Bezug auf die Nebenwirkungen und die Effektivität von Brustkrebstherapien führt. Vor allem bei dosis-dichten (dd) oder dosis-intensivierten Chemotherapieregimen wird diese Patientinnengruppe vernachlässigt. **Patienten und Methode:** In der vorliegenden Analyse werden Daten aus 4 deutschen, randomisierten, (neo)adjuvanten, anthrazyklinbasierten Studien ausgewertet hinsichtlich der Toxizität, Compliance und Machbarkeit. Die Patientinnen wurden entsprechend ihres Alters in 3 Kategorien unterteilt. **Ergebnisse:** Von den 4775 eingeschlossenen Patientinnen waren 73,5% < 60 Jahre, 15,8% 60–64 Jahre und 10,6% > 64 Jahre alt. Die Compliance nahm mit zunehmendem Alter ab, die Rate der Therapieunterbrechungen nahm signifikant zu ($p < 0,001$). Die Rate der Dosisreduzierungen stieg mit zunehmendem Alter an bei Patientinnen, die Docetaxel/Doxorubicin/Cyclophosphamide (TAC) ($p_{overall} = 0,02$) und Patientinnen, die 5-Fluorouracil/Epirubicin-Cyclophosphamide ($FE_{120}C$) erhielten. Neutropenien Grad 3 + 4 entstanden bei Patientinnen > 64 Jahren häufiger bei $FE_{120}C$ (77%) als bei TAC (55%) trotz G-CSF-Gabe. Die Inzidenz der febrilen Neutropenien war bei Regimen ohne zusätzliches Taxan am geringsten. **Zusammenfassung:** Das Ausmaß und die Intensität der Nebenwirkungen stiegen mit zunehmendem Alter an. Neutropenien stiegen in den dd-Gruppen nicht signifikant an, die höchste Rate wurde bei $FE_{120}C$-Patientinnen beobachtet. $FE_{120}C$ ohne G-CSF bei Patientinnen > 64 Jahren scheint keine Therapiemöglichkeit zu sein.

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Introduction

More than 50% of all breast cancers (BCs) are diagnosed in patients older than 65 years. Because elderly patients are underrepresented in clinical trials, level 1 evidence on treatment for this population is scarce. Treatment recommendations for younger women cannot simply be carried over to elderly patients [1–3], but undertreatment could lead to higher rates of BC recurrences and mortality [4, 5].

Various study groups have published retrospective analyses, showing that older patients derive the same benefit from standard chemotherapy as younger patients [5, 6]. Muss et al. [7] demonstrated that adjuvant chemotherapy (cyclophosphamide, methotrexate, and fluorouracil) is superior to capecitabine monotherapy in patients > 65 years, suggesting that elderly women need to be treated according to standard treatment recommendations. 4 cycles of 3-weekly epirubicin/cyclophospamide are no longer considered the standard of care, especially in patients with node-positive BC.

Several meta-analyses [8] have shown that the overall outlook for women diagnosed with early BC has improved in recent decades. Anthracyclines are still considered to be one of the most potent cytotoxic drugs for BC patients. Our study group has already shown that elderly patients are able to cope with a variety of taxane-containing regimens [9]. A major issue in treating elderly patients with chemotherapy is toxicity. Bone marrow reserves and renal function decrease with age, increasing the probability of myelosuppression and the risk of toxicity. The occurrence of myelosuppression, cardiodepression, peripheral neuropathy, and neurotoxicity can complicate treatment [10, 11].

The aim of this analysis was to compare data on acute toxicity and tolerability in different age groups with a focus on the elderly population receiving modern anthracycline- and taxane-containing chemotherapy for BC.

Materials and Methods

Data from 4 German prospectively randomized clinical trials, conducted between 1999 and 2005, were pooled. These trials included primary BC patients receiving anthracycline-containing chemotherapy. The meta-database was closed in October 2006; the number of patients in the present analysis may, therefore, differ from the respective individual study publications. For every study the number of patients included in the present analysis exceeds 75% of those evaluable. Toxicity data from the studies were analyzed for anthracycline-containing chemotherapy regimes in older patients (aged > 64 years) and were compared with toxicity data from patients aged < 60 and those aged 60–64 years treated in the same studies. Patients older than 64 years were described as 'elderly' patients in line with the publications [12, 13].

In the ADEBAR trial (NCT00047099), patients received 4 cycles of adjuvant therapy either with epirubicin/cyclophosphamide (90/600 mg/m^2) every 3 weeks (q3w) followed by 4 cycles of docetaxel (100 mg/m^2) q3w, or 6 cycles of 5-fluorouracil/epirubicin (500/60 mg/m^2) intravenously (i.v.) on days 1 and 8, and cyclophosphamide (75 mg/m^2) orally (p.o.) on days 1–14 q4w [14, 15]. The enrolment into the study was limited to patients aged ≥ 18 to ≤ 70 years with a life expectancy of at least 32 months. The patients only received secondary prophylaxis with granulocyte colony-stimulating factors (G-CSF) if febrile, severe or prolonged neutropenia occurred.

In the ASG 1–3 trial (NCT00668616), patients received 4 cycles of adjuvant therapy either with epirubicin/cyclophosphamide (90/600 mg^2) q3w followed by 4 cycles of paclitaxel (175 mg^2) q3w, or 4 cycles of epirubicin (120 mg/m^2) q2w and then 4 cycles of paclitaxel (175 mg/m^2) q2w. Enrolment into the study was limited to patients aged ≥ 18 to ≤ 75 years. Patients in the dose-dense (dd) arm receiving doxorubicin/docetaxel (AT) were given a primary prophylaxis with G-CSF on days 5–10. Patients with primary anti-infective therapy were not included in the study.

In the GeparDuo trial (NCT00543829), patients received 4 cycles of neoadjuvant therapy with doxorubicin/cyclophosphamide (60/600 mg/m^2) q3w followed by 4 cycles of docetaxel (100 mg/m^2) q3w or 4 cycles of AT (50/75 mg/m^2) q2w [16]. Enrolment into the study was limited to patients aged ≥ 18 years and with a life expectancy of ≥ 10 years. All patients in the dd arm who received AT q2w were given primary prophylaxis with G-CSF on days 5–10. Antibiotic treatment was started only as a secondary prophylaxis.

In the GeparTrio trial (NCT00544765), patients received 2 cycles of neoadjuvant chemotherapy with docetaxel/doxorubicin/cyclophosphamide (TAC, 75/50/500 mg/m^2) followed by either 4 cycles of TAC, 6 cycles of TAC, or 4 cycles of vinorelbine (25 mg/m^2 on days 1 and 8) plus capecitabine (1,000 mg/m^2 on days 1–14) q3w [17, 18]. Enrolment into the study was limited to patients aged ≥ 18 years, with no upper age limit. In this trial, the supportive treatment has been amended during the course of the trial, starting with only antibiotic prophylaxis. The febrile neutropenia (FN) prophylaxis regimen was stepwise intensified to G-CSF, pegfilgrastim and pegfilgrastim plus ciprofloxacin [19].

Dose delays and dose reductions were performed according to special steps predefined in the protocol. In the following, when the term 'compliance' is used, it refers to the adherence to the planned chemotherapy as defined in the individual protocols, in terms of dose reduction, dose discontinuation and dose delays in total. In this paper, only the anthracycline-containing cycles were analyzed. Further details regarding the study designs have been described elsewhere [9].

The chemotherapy schedules were grouped as follows:

- TAC: Docetaxel/doxorubicin/cyclophosphamide i.v. q3w;
- Canadian $FE_{120}C$: 5-fluorouracil/epirubicin i.v. days 1 and 8 followed by cyclophosphamide p.o. days 1–14 q4w;
- A(E)C-[T/P]: doxorubicin(epirubicin)/cyclophosphamide (60(90)/600 mg/m^2) i.v. q3w followed by docetaxel (100 mg/m^2) or paclitaxel (175 mg/m^2) q3w;
- ddAT: dd doxorubicin/docetaxel (50/75 mg/m^2) q2w;
- ddE-ddP: dd epirubicin followed by paclitaxel (120/175 mg/m^2) q2w.

The protocols were reviewed by all responsible local ethics committees and competent authorities. All patients gave written informed consent for participating in the individual trials.

Data Collection and Statistical Analyses

Data on dose delays and dose reductions, hospitalizations, treatment discontinuations, deaths, and hematological and non-hematological toxicities were collected. For hematological toxicity, not all records of all cycles included the same data on the respective events: FN data were recorded for patients on the TAC regimen; all other patients were considered to have FN of at least grade 3 in a given chemotherapy cycle if they had grade 3+4 neutropenia, more than grade 1 fever, and no infection. All FN cases reported as serious adverse events with severity grade were also considered. In cycles where at least 1 of the 3 parameters (neutropenia, fever, infection) was missing, and FN was not reported in the serious adverse events description, the cycle was considered as having a missing value for FN. All statistical analyses were exploratory and no adjustments were made for multiple comparison. Calculations were performed using

SPSS 14.0.1 for Windows (SPSS Inc. Chicago, IL, USA). Grading systems for toxicities in different studies were checked for consistency and were converted into National Cancer Institute Common Terminology Criteria version 3 (NCI-CTCAE 3.0) grades. Pearson's chi-squared test was performed to compare incidences of toxicity endpoints.

Results

This analysis is based on data from 4 German studies including a total of 4,775 patients receiving an anthracycline-containing chemotherapy regimen for primary BC. A total of 22,306 anthracycline-containing chemotherapy cycles were administered, 74.8% (n = 16,679) to patients aged < 60 years, 15.2% (n = 3,389) to patients between 60 and 64 years and 10% (n = 2,238) to patients aged > 64 years. The main baseline characteristics are summarized in table 1.

Dose Delays, Dose Reductions, and Early Discontinuations

Dose delays were reported in 10.2% and treatment discontinuations due to toxicity in 10.3% of all patients who started treatment. The $FE_{120}C$ regimen was the most toxic with dose reduction of 21.5% in total (15.7% in the < 60, 26.9% in the 60–64, and 39.9% in the > 64 year age groups; p < 0.001), dose delays of 26.8% in total (24.7% in the < 60, 32.4% in the 60–64, and 28.6% in the > 64 year age groups; p = 0.266) and early treatment discontinuation of 16.6% in total (13.2% in the < 60, 20.2% in the 60–64, and 26.8% in the > 64 year age groups; p = 0.007).

Table 1. Baseline characteristics of the whole population

	Group			Total
	< 60 years	60–64 years	> 64 years	
Median age, years (range)	47	62	67	51 (23–80)
n (%)	3,516 (73.6)	753 (15.8)	506 (10.6)	4,775
ECOG (valid %)				
0	87.9	74.4	73.1	84.2
1	11.9	25.6	26.1	15.5
2	0.2	0.0	0.8	0.3
3	0.0	0.0	0.0	0.0
Hormone receptor status (%)				
Positive	62.9	70.9	67.0	64.6
Negative	27.2	21.9	26.3	26.3
Unknown	9.8	7.2	6.7	9.1
Tumor grading (valid %)				
1	4.7	5.0	5.9	4.9
2	54.9	55.1	57.5	55.2
3	40.4	39.9	36.6	39.9
Pathology (valid %)				
Ductal invasive	76.8	70.6	73.7	75.5
Lobular invasive	15.6	20.3	17.4	16.5
Others	7.6	9.1	8.8	8.0
Tumor size (valid %)				
1	14.3	14.2	16.6	14.6
2	66.1	63.0	59.2	64.9
3	13.9	14.2	12.8	13.9
4	5.6	8.5	11.4	6.7
Nodal status (valid %)				
pN positive	31.5	37.2	39.2	33.2
pN negative	0.1	0.0	0.0	0.0
cN positive	31.7	26.7	24.7	30.1
cN negative	36.8	36.1	36.0	36.6
Her2 status (%)				
Positive	20.4	18.9	17.0	19.8
Negative	48.6	50.6	52.0	49.3
Unknown	31.0	30.5	31.0	30.9

ECOG = Eastern Cooperative Oncology Group, valid % = exclusion of the missing values.

Comparing the dd regimens with each other, the overall dose delays were comparable with the 9.1% for the ddAT schedule and 9.6% for the ddE-ddP schedule. The reported incidences of dose delays during ddAT steadily increased with age (5.8% in the < 60, 17.3% in the 60–64, and 20.0% in the > 64 year age groups; p overall < 0.001), whereas during the ddE-ddP regimen there was no significant differences between the age groups (9.1%, 14.5%, and 7.0% respectively).

Hematological Toxicity

The rate of neutropenia grade 3+4 and FN for the applied regimens are given in table 2. The incidence of these hematological toxicities varied by regimen and age. More-intense regimens such as $FE_{120}C$ were associated with more grade 3–4 hematological toxicity than less-intense regimens such as A(E)C-[T/P]. Analyzing older versus younger patients, the per-patient incidence of grade 3–4 hematological adverse events generally increased with age, regardless of the chemotherapy regimen administered. The rate of neutropenia grade 3–4 increased significantly from the younger to the elderly group. Results comparable to the rate of neutropenia grade 3+4 were found for the rate of leukopenia grade 3+4, which also showed a significant increase with age. The rates of FN were not significantly different between the age groups.

The incidence of FN of all grades was lowest in the regimens without an additional taxane ($FE_{120}C$ regimen with 2.9%, ddE-ddP regimen with 0.9% and A(E)C-[T/P] with 1.0% for all patients) in comparison to the TAC (10%) and the ddAT schedule (4.7%). Further details for neutropenia and FN grade 3+4 according to the patients' age are summarized in table 2.

Non-hematological Toxicity

Not all non-hematological toxicities were recorded consistently for each chemotherapy regimen and all cycles in the individual trials. A summary of the reported events with regards to the different age groups are shown in table 3. The non-hematological toxicities included nausea, vomiting, diarrhea, stomatitis, sensory neuropathy and changes in kidney or liver function. Non-hematological toxicities varied less between the age groups.

Diarrhea grade 1–4 was less frequently reported when an anthracycline monotherapy was administered. The overall incidence of sensory neuropathy of any grade was higher in anthracycline- and taxane-containing schedules such as TAC (47.3%) and ddAT (46.0%) than in $FE_{120}C$ (21.5%), A(E)C-[T/P] (18.7%), and ddE-[ddP] (16.8%) where anthracyclines were given without concurrent taxanes.

Discussion

In this pooled retrospective analysis of individual patient data from 4 randomized clinical trials, we describe the compliance, and hematological, and non-hematological side effects of 5 different anthracycline-containing chemotherapy regimens for women with primary BC, with the focus on the elderly population. The analysis separated the toxicities according to patients' ages into 3 groups: patients of < 60, those between 60 and 64 and those > 64 years. Elderly patients were defined by age > 64 years.

Overall, the compliance decreased with age, independent of the applied chemotherapy regimens. The $FE_{120}C$ schedule

Table 2. Incidences of hematological toxicity

	Age groups, years				Overall p value
	< 60	60–64	> 64	Total	
Neutropenia grade 3+4*					
n	1,243	362	278	1,883	
Treatment, %					
TAC	37.5	56.7	55.2	43.0	< 0.001
Canadian $FE_{120}C$	67.0	62.6	76.5	67.7	0.127
A(E)C-[T/P]	52.8	52.0	65.5	54.2	0.012
ddAT	43.5	47.4	43.6	44.2	0.815
ddE-ddP	29.7	36.7	33.3	31.1	0.599
Febrile neutropenia grade 3+4*					
n	172	43	30	245	
Treatment, %					
TAC	9.3	11.3	14.3	10.0	0.088
Canadian $FE_{120}C$	2.5	4.7	2.4	2.9	0.498
A(E)C-[T/P]	1.0	0.5	1.4	1.0	0.686
ddAT	4.5	5.1	5.1	4.7	0.960
ddE-ddP	0.0	6.4	0.0	0.9	< 0.001

F = 5-fluouracil, A: adriamycin, E = epirubicin, C = cyclophosphamide, T = docetaxel, P = paclitaxel, dd = dose dense.
*According to the National Cancer Institute Common Toxicity Criteria.

Table 3. Incidences of non-hematological side effects

	Age groups, years				Overall p value
	< 60	60–64	> 64	Total	
Fatigue grade 3+4*					
Treatment, % (n)					
TAC	11.6 (175)	12.7 (34)	17.1 (29)	12.2 (238)	0.113
Canadian $FE_{120}C$	–	–	–	–	–
A(E)C-[T/P]	8.5 (28)	11.8 (8)	16.0 (8)	44 (9.8)	0.208
ddAT	24.7 (81)	39.5 (32)	35.0 (14)	28.3 (127)	0.018
ddE-ddP	–	–	–	–	–
Stomatitis grade 3+4*					
Treatment, % (n)					
TAC	3.6 (54)	3.7 (10)	5.9 (10)	3.8 (74)	0.328
Canadian $FE_{120}C$	6.8 (24)	9.3 (10)	14.5 (12)	8.4 (46)	0.073
A(E)C-[T/P]	1.2 (12)	0.4 (1)	2.4 (4)	1.2 (17)	0.203
ddAT	2.8 (9)	7.4 (6)	5.0 (2)	3.8 (17)	0.133
ddE-ddP	2.1 (6)	13.2 (7)	11.9 (5)	4.8 (18)	< 0.001
Diarrhea grade 3+4*					
Treatment, % (n)					
TAC	3.5 (53)	3.4 (9)	8.2 (14)	3.9 (76)	0.010
Canadian $FE_{120}C$	1.4 (5)	3.7 (4)	2.4 (2)	2.0 (11)	0.321
A(E)C-[T/P]	0.4 (4)	0.0 (0)	0.0 (0)	0.3 (4)	0.446
ddAT	8.3 (27)	7.4 (6)	2.5 (1)	7.6 (34)	0.430
ddE-ddP	0.7 (2)	0.0 (0)	0.0 (0)	0.5 (2)	0.711
Sensory neuropathy grade 3+4*					
Treatment, % (n)					
TAC	1.1 (17)	2.2 (6)	1.8 (3)	1.3 (26)	0.303
Canadian $FE_{120}C$	0.6 (2)	0.0 (0)	0.0 (0)	0.4 (2)	0.581
A(E)C-[T/P]	0.1 (1)	0.0 (0)	0.0 (0)	0.1 (1)	0.817
ddAT	0.9 (3)	2.5 (2)	0.0 (0)	1.1 (5)	0.384
ddE-ddP	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–
Increase of liver enzymes grade 3+4*					
Treatment, % (n)					
TAC	2.3 (34)	2.3 (5)	2.0 (3)	2.2 (42)	0.981
Canadian $FE_{120}C$	2.1 (7)	1.9 (2)	2.5 (2)	2.1 (11)	0.960
A(E)C-[T/P]	2.1 (20)	2.3 (5)	0.0 (0)	1.9 (25)	0.183
ddAT	1.8 (6)	5.0 (4)	7.5 (3)	2.9 (13)	0.064
ddE-ddP	10.3 (28)	3.8 (2)	0.0 (0)	8.3 (30)	0.050
Increase of creatinine grade 3+4*					
Treatment, % (n)					
TAC	4.5 (68)	9.3 (25)	9.5 (16)	5.6 (109)	< 0.001
Canadian $FE_{120}C$	–	–	–	–	–
A(E)C-[T/P]	0.5 (3)	2.4 (3)	1.2 (1)	0.9 (7)	0.124
ddAT	1.2 (4)	1.3 (1)	2.5 (1)	1.4 (6)	0.804
ddE-ddP	0.0 (0)	3.7 (2)	8.6 (3)	1.4 (5)	< 0.001

F = 5-fluouracil, A: adriamycin, E = epirubicin, C = cyclophosphamide, T = docetaxel, P = paclitaxel, dd = dose dense.
*According to the National Cancer Institute Common Terminology Criteria (Version 3 Terminology).

was most problematic with a particularly high incidence of dose delays, dose reductions, and therapy discontinuations. This was seen for the elderly in our analysis as well as in studies of other groups [20, 21]. Nevertheless, some authors found in a retrospective analysis that age per se was not an indicator for decreasing compliance, which appeared to be related to co-morbidities and BC stage [22].

Hematological toxicities increased with age. The lowest incidence of hematological side effects was noticed for neutropenia and FN in the ddE-ddP schedule, despite the dd regimen. The highest incidence of neutropenia was reported for patients receiving $FE_{120}C$. The highest rate of FN was reported for TAC. The toxicity of ddAT or $FE_{120}C$ was in agreement with the findings of other study groups, who reported similarly high results of adverse hematological events, which also increased in the elderly [21, 23].

The high rate of hematological side effects can be countered with G-CSF. This was used in the dd regimens (ddAT, ddE-ddP) as a primary prophylaxis, and stepwise in patients receiving TAC to help them adhere to the appropriate and most effective dosing [24] that is part of many clinical trials [25–27]. No primary prophylaxis was implemented in the ADEBAR trial, but secondary prophylaxis with G-CSF was given to more than 60% [28] of those receiving $FE_{120}C$. The European Organisation for Research and Treatment of Cancer (EORTC) guidelines [29] recommend primary prophylaxis with G-CSF when the risk for FN of the regimen is 20%, or when the FN risk of the regimen is between 10 and 20% in high-risk patients (e.g. > 65 years). Age is the most notedd risk factor for FN.

In our cohort, the frequency and severity of non-hematological side effects were as expected from the known side-

effect profile of the agents used. Sensory neuropathy grade 3+4 occurred more often in patients receiving a taxane-containing therapy. The elderly do not necessarily suffer more from those side effects, as the comparison between the age groups did not show significant differences. Mucositis grade 3+4 was less frequently reported in patients receiving A(E)C-[T/P] than in patients receiving any kind of dd or dose-intensified therapy. The elderly patients seemed to suffer more from mucositis grade 3+4 than younger patients, but only the ddE-ddP regimen showed significant differences between the age groups, with a peak between 60 and 64 years.

There are no follow-up data available for this analysis. Therefore, the final results regarding long-term toxicities are missing. In addition, there are no data available on relapses or responses [16, 18, 28, 30]. The analysis has its limitations as it has been done as a post-hoc analysis. Long-term toxicity is lacking and the toxicity data have not been linked to outcome data. However, the large sample size supports the findings. However, the number of patients who were 65 and older was low, despite the fact that only 1 study had an age limit of 65 years. This reflects current clinical trial practice for elderly patients. We have therefore started a trial with elderly patients comparing a taxane-containing combination therapy with 4 cycles of conventional epirubicin/cyclophospamide [31].

In conclusion, the dd and dose-intensified regimens induced more side effects. Our analysis showed that all analyzed age groups were able to cope with the therapeutic approaches. Elderly patients experienced more hematological side effects with the analyzed chemotherapies. However, not all of the elderly patients have received G-CSF as recommended by current guidelines. In general, sequential therapies were better tolerated than combination therapies, and dd therapies were also well tolerated in a sequential application design with the backup of G-CSF if necessary. $FE_{120}C$ is an effective regimen but, after evaluating the risk benefit, it does not seem to be an adequate alternative to sequential taxane-containing regimen especially in those > 64 years.

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