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G-CSF in the Prevention of Febrile Neutropenia in Chemotherapy in Breast Cancer Patients

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Key Words

Breast cancer · Neutropenia, febrile · G-CSF · Prevention · Chemotherapy · Complications

Summary

The most common chemotherapeutic agents in the treatment of breast cancer are anthracyclines and taxanes. The major dose-limiting toxicities associated with these agents are myelosuppression and associated febrile neutropenia (FN). FN can significantly impact the ability to deliver full-dose chemotherapy on schedule and as a result may increase the risk of disease recurrence and eventual disease-related mortality. The use of granulocyte colony stimulating factors (G-CSFs) significantly improves the management of FN, both in a therapeutic and in a prophylactic approach. Nevertheless, the high cost of these agents limits their widespread prophylactic use. Therefore, the identification of patients who are at a higher risk of developing FN and who will benefit from the prophylactic use of G-CSFs has become the subject of several clinical and cost-effectiveness studies. Recently, new data have been accumulated concerning the risk of FN in different chemotherapy regimens, and different risk models have been developed to assess the neutropenic risk with all its complications. This article reviews and summarizes cutting-edge, disease-specific data as well as national and international guidelines regarding the use of G-CSFs to prevent chemotherapy-induced FN, with focus on the treatment of breast cancer.

Schlüsselwörter

Brustkrebs · Neutropenie, febrile · G-CSF · Prävention · Chemotherapie · Komplikationen

Zusammenfassung

Die am häufigsten in der Therapie des Mammakarzinoms verwendeten Chemotherapeutika sind derzeit Anthrazykline und Taxane. Die wichtigsten dosislimitierenden Toxizitäten dieser Medikamente sind Myelosuppression und febrile Neutropenie (FN). FN kann einen signifikanten Einfluss auf die planmäßige Verabreichung der chemotherapeutischen Gesamtdosis haben und infolgedessen das Risiko für Rezidiv und krankheitsbedingte Sterblichkeit erhöhen. Der Einsatz Granulozytenkolonie-stimulierender Faktoren (G-CSFs) in der klinischen Routine führt zur Verbesserung des Managements der FN sowohl in therapeutischer als auch in prophylaktischer Hinsicht. Dennoch wird der breite prophylaktische Einsatz von G-CSFs durch ihre hohen Kosten eingeschränkt. Die Identifizierung derjenigen Patienten, die ein erhöhtes Risiko für die Entwicklung einer FN haben und daher von einer prophylaktischen G-CSF-Anwendung besonders profitieren würden, ist Thema verschiedener aktueller klinischer und Kosteneffizienz-Gesichtspunkte berücksichtigender Studien. In letzter Zeit wurden neue Daten bezüglich des FN-Risikos bei verschiedenen Chemotherapie-Regimen gesammelt und unterschiedliche Risikomodelle entwickelt, um die Gefahr einer Neutropenie mit all ihren Komplikationen zu bewerten. Vor diesem Hintergrund fasst die vorliegende Arbeit aktuelle Daten und entsprechende Empfehlungen nationaler und internationaler Fachgesellschaften zum Einsatz von G-CSFs für die Prävention chemotherapieinduzierter febriler FN bei Brustkrebs zusammen.

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Introduction

The major dose-limiting toxicities associated with systemic chemotherapy are myelosuppression and associated febrile neutropenia (FN). In general, FN is treated with immediate hospitalization and administration of intravenous (i.v.) antibiotics. Thus, FN remains a major clinical problem in oncological therapy, as it is associated with prolonged hospital stay, increased monitoring, diagnostic and therapy-associated costs and reduced quality of life. In this review, we focus on FN in breast cancer therapy, since this disease is very common and can potentially be cured by modern chemotherapy [1], particularly in the adjuvant setting. Therefore, maintaining an adequate dose intensity is critical for patient survival.

Febrile Neutropenia in Breast Cancer Therapy

While the reported mortality associated with FN appears relatively low (approximately 4%) [2, 3], FN can significantly impact the ability to deliver full-dose chemotherapy on schedule [4–7]. The importance of chemotherapy dose intensity with regard to long-term disease control and survival in patients with breast cancer is supported by preclinical data, retrospective analyses and prospective studies. It was shown that reduction in chemotherapy dose intensity may result in increased risk of disease recurrence and disease-related mortality [4, 8–12]. The incidence of FN varies considerably across treatment regimens used in breast cancer patients and approaches 25–40% while being greater in elderly cancer patients [2, 13, 14]. The risk of developing FN is driven both by the chemotherapy regimens and by patient-related factors. It is known that some chemotherapy regimens are more myelotoxic than others. Thus, the risk of FN is greater in anthracycline-containing regimens, such as AC (doxorubicin, cyclophosphamide) or CAF (cyclophosphamide, doxorubicin, fluorouracil) than for example in CMF (cyclophosphamide, methotrexate, fluorouracil) [3, 14]. High chemotherapy dose intensity is also a risk factor for FN. Dale et al. [15] tried to analyze the risk for commonly used chemotherapy regimens, but found that rates for FN were reported infrequently and when reported, varied greatly for the same or similar regimens. In the absence of clearly defined, regimen-specific risks, assessing patient-specific risk factors in each patient may have greater value in determining patients for which supportive intervention would be appropriate.

Different risk models have been developed to assess the neutropenic risk with all its complications. In their systematic review of 18 published risk models for predicting chemotherapy-induced neutropenia and its consequences, Lyman et al. [14, 16] found that age, poor performance status, nutritional status, chemotherapy dose intensity and low baseline blood cell counts were significantly associated with the risk of severe and febrile neutropenia or reduced chemotherapy dose intensity in multivariate analyses of 2 or more studies. Some authors identified advanced cancer stage and prior chemotherapy as additional risk factors for development of severe neutropenic complications including FN [13]. The role of age in the susceptibility to neutropenic complications has been explored particularly intensely. At least 10 studies have found higher age to be an independent risk factor for complications such as FN in patients receiving cancer chemotherapy [17]. Indeed, increasing age was a significant independent predictor in multivariate models of risk of FN across a number of adjuvant breast cancer treatment regimens among approximately 20,000 women studied retrospectively in the US [14]. Also, patients aged 65 or over are more likely to receive less than 85% of the standard reference dose intensity than patients aged under 65, due to neutropenic complications [18]. Age was also a significant predictor of serious medical complications, including death of patients with FN, evaluated by the Multinational Association of Supportive Care of Cancer scoring system [19]. Moreover, Balducci and Extermann [20] were able to show that the number of treatment-related deaths varying between 5–30% is higher in elderly patients (> 70 years of age) compared to those aged under 69 (3–8%) [2, 3].

Granulocyte Colony Stimulating Factor (G-CSF) as a Therapeutic Option

In 1991, the recombinant human granulocyte colony stimulating factor (G-CSF), filgrastim, was approved by the FDA as a preventive agent to decrease the incidence of infection and FN in patients treated with myelosuppressive chemotherapy [21]. Since then, several clinical studies have demonstrated that prophylactic use of G-CSF can reduce the incidence of FN, documented infections, infection-related hospitalization with i.v. antibiotic use and dose reduction or delay in the treatment of several malignancies including breast cancer [22, 23]. The prophylactic use of G-CSFs can be categorized as primary prophylaxis (i.e. initiation of a G-CSF before the advent of neutropenia) or secondary prophylaxis (i.e. initiation of G-CSF in cycles of chemotherapy subsequent to the chemotherapy-induced prolonged neutropenia or neutropenic fever).

Several trials were performed to evaluate the effectiveness of G-CSFs in reducing the risk of FN. A prospective randomized study designed to prove whether the addition of lonidamine or G-CSF increases the efficacy of EC (epirubicin, cyclophosphamide) in the treatment of patients with early breast cancer documented a significant decrease in FN among patients in the G-CSF arms (1.2 and 6.6% of patients in the G-CSF and control arms, respectively; $p = 0.004$). However, hematological toxicity was not significantly dose-limiting, and, as a consequence, no differences were observed between the G-CSF and control arms regarding dose-intensity, disease-free survival (DFS) and overall survival (OS). These data suggest that any small reduction of an adequate dose of chemotherapy does

not compromise the survival of patients with early breast cancer [24]. Prophylactic G-CSF has also been successfully used in various chemotherapy regimens for patients with metastatic disease. In patients with chemotherapy-naive metastatic breast cancer, G-CSF significantly reduced the incidence of FN when administered with time-intensified FEC (5-fluorouracil (5-FU), epirubicin, cyclophosphamide; 500, 75 and 500 mg/m^2 every 14 days) compared to standard-dose FEC [25]. G-CSF also demonstrated its effectiveness in reducing the rate of FN in a randomized, double-blind, phase III trial designed to compare filgastrim and leridistim (formerly myelopoietin), a chimeric dual agonist that binds both G-CSF and IL-3 receptors, for the prevention of neutropenic complications in patients with breast cancer receiving TAC (docetaxel, doxorubicin, cyclophosphamide) chemotherapy. In this trial, the incidence of FN was 7% in the G-CSF arm, 19% in the daily leridistim arm ($p = 0.003$ for comparison with G-CSF) and 22% in the alternate-day leridistim arm ($p < 0.001$ for comparison with G-CSF) [26]. In addition, in a study comparing the efficacy of 2 different schedules of epirubicin and paclitaxel as first-line chemotherapy in patients with advanced breast cancer, addition of G-CSF also resulted in a reduced rate of FN (4% with G-CSF vs. 9% without G-SCF, $p = 0.24$) [27]. Prophylactic G-CSF use in other chemotherapy regimens for patients with metastatic disease, such as docetaxel alone or in combination with either vinorelbine, epirubicin or cisplatin, also resulted in significant reduction of the FN rate and allowed dose-intensive administration of these chemotherapeutics [26, 28–31].

The relatively short half-life of filgrastim, which necessitates daily dosing until neutrophil recovery led to development of a long-acting pegylated form of filgrastim, pegfilgrastim. In a double-blind, placebo-controlled phase III study using pegfilgrastim from the first cycle of docetaxel 100 mg/m^2, the rate of FN in the placebo group was 17% compared with 1% in the pegfilgrastim group, and the rate of hospitalization and i.v. antibiotic use was reduced by 80% [32]. At the same time, it was shown that single-agent docetaxel at a dose of 100 mg/m^2 every 21 days is associated with a 10–20% incidence of FN in the absence of growth factor [33, 34]. In the pivotal pegfilgrastim studies comparing a single dose of pegfilgrastim with daily G-CSF support in women with primary and metastatic breast cancer receiving doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 administered every 3 weeks, the rate of FN in the filgrastim group was 19–20% compared with 11–13% in the pegfilgrastim groups [35, 36]. The expected FN rate using the same chemotherapy regimen would have been approximately 50% without growth factor support [37].

In general, G-CSFs have a low toxicity profile and therefore are well tolerated. Across all clinical studies conducted to date, the most frequent adverse event with both pegfilgrastim and filgrastim was mild to moderate bone pain which occurred in 20–30% of patients [38, 39]. Toxicities such as fever, rash, injection-site reaction, fatigue, vomiting, diarrhea and dyspnea are rare and more often associated with GM (granulocyte-macrophage)-CSFs use [38, 39, 40]. Whether G-CSFs by themselves or in combination with more dose-intense chemotherapy regimens may increase the risk of secondary leukemia in breast cancer patients, remains controversial [40, 41].

Risk-Benefit Analysis and Health-Economic Issues

The efficacy data from the studies discussed above demonstrated that primary administration of G-CSFs can reduce the incidence of FN by approximately 50–90% [13] and are thus supportive of a prophylactic use of G-CSF. Nevertheless, cost issues are likely to play a major role in limiting its wide prophylactic use. The cost of G-CSFs together with their increasingly broad clinical application has promoted a number of health-economic analyses. Based on the limited information concerning general costs associated with FN, G-CSF use was found to be cost-saving in patients treated with chemotherapy regimens associated with a FN rate of 40% or more [42, 43]. Based on this model and the clinical data showing that the use of G-CSFs only has a small to no impact on DFS and OS, the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) recommended primary administration of G-CSFs only in patients with an expected FN incidence of > 40% [13, 23]. Subsequent models based on more complete estimates of direct medical costs as well as indirect and out-of-pocket expenses suggest that a more reasonable threshold for a cost-saving use of G-CSF is in the range of a 18–23% FN rate [3].

It is estimated that primary prophylaxis would result in unnecessary treatment of 60–80% of patients who would not have developed FN during their chemotherapy treatment. This provided the rationale for secondary G-CSF administration in patients with a prior episode of FN. Indeed, the results of several trials confirmed that use of G-CSFs in subsequent chemotherapy cycles after documented occurrence of FN in an earlier cycle can decrease the probability of FN in these cycles and allow maintenance of the planned dose intensity [2]. However, in the absence of clinical data demonstrating DFS or OS benefits when using secondary G-CSF prophylaxis, the ASCO 2000 guideline for the use of G-CSFs recommends chemotherapy dose reduction after neutropenic fever should be considered as the first therapeutic option, with the exception of curable tumors [13]. To date, no single trial has been large enough to examine the effects of G-CSFs on infection-related or disease-related mortality [2]. The use of G-CSFs for secondary prophylaxis is also limited by the fact that the FN risk is greatest in the earliest cycle. This finding comes from a study with older patients with aggressive non-Hodgkin's lymphoma who were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), where 63% of the toxic deaths (mostly neutropenia-related) occurred in the first cycle of the 6- to 8-cycle regimens [44]. Also, in patients with

Table 1. Incidence of FN associated with selected chemotherapy regimens without CSF support

Chemotherapy regimen	FN, %	Reference
Non-anthracycline regimens		
CMF with C oral d1–14 (100/40/600 mg/m^2 d1, d8, q28)	1	Leonard, 2003 [5]
	6	Levine, 1998 [58]
CMF (600/40–50/600 mg/m^2 d1, d8, q28)	8	Leonard, 2003 [5]
CMF (600–750/40/600 mg/m^2, q21)	1	Leonard, 2003 [5]
Anthracyclines		
A→CMF (75/600/40/600 mg/m^2, q21)	11	Leonard, 2003 [5]
FEC (600/60/600 mg/m^2, q21)	0	Leonard, 2003 [5]
CEF with C, oral d1–14 (500/60/75 mg/m^2 d1, d8, q28)	8.5	Levine, 1998 [58]
FEC-HD (750mg/m^2 d1–4, 35/400 mg/m^2 d2–4, q21)	50	Chevallier, 1995 [28]
E→CMF (100 mg/m^2, q21, 600/40/600 mg/m^2 d1–8, q28)	8	Leonard, 2003 [5]
CAF (600/60/600 mg/m^2, q21)	4	Wood, 1994 [8]
CAF (500/50/500 mg/m^2, q21)	5	Jassem, 2001 [59]
	29	Leonard, 2003 [5]
AC (60/600 mg/m^2, q21)	9–10	Biganzoli, 2002 [54]
A (60 mg/m^2, q 21)	7	Norris, 2000 [60]
A/vinorelbine (50 mg/m^2 d1/25 mg/m^2 d1, d8, q21)	27	Norris, 2000 [60]
A/vinorelbine (40 mg/m^2 d1/20 mg/m^2 d1, d8, q21)	12	Norris, 2000 [60]
Taxanes		
Paclitaxel (175 mg/m^2, q21)	2–4	Nabholtz, 1996 [61]
T (100 mg/m^2, q21)	38	Hudis, 1996 [62]
	17	Vogel, 2005 [32]
	21	O'Shaughnessy, 2002 [53]
T (75mg/m^2, q21)/capecitabine (1.25 mg/m^2 oral)	16	O'Shaughnessy, 2002 [53]
T/cisplatin (75/80 mg/m^2, q21)	24	Spielmann, 1999 [63]
T/vinorelbine (60/30 mg/m^2, q14)	34	Mayordomo, 2004 [64]
T/vinorelbine (60/25 mg/m^2, q14)	14	Gomez-Bernal, 2003 [65]
Anthracyclines + taxanes		
A/paclitaxel (60/175 mg/m^2, q21)	23	Gianni, 1995 [50]
	32	Biganzoli, 2002 [54]
A/paclitaxel (50/220 mg/m^2, q21)	8	Jassem, 2001 [59]
AC→T (60/600/100 mg/m^2, q21)	25	Perez, 2002 [49]
T→AC (100/60/600 mg/m^2, q21)	40	Perez, 2002 [49]
TAC (75/50/500 mg/m^2, q21)	34	Nabholtz, 2001 [51]
ATC (60/60/600 mg/m^2, q21)	38	Smith, 2002 [66]
TA (75/50 mg/m^2, q21)	50	Misset, 1999 [37]
	33	Nabholtz, 2003 [67]

FN = Febrile neutropenia, CSF = colony stimulating factor, T = docetaxel, A = doxorubicin, C = cyclophosphamide, M = methotrexate, F = 5-FU, E = epirubicin, HD = high-dose, q21/28 = every 21/28 days, d = day.

advanced breast cancer who were treated with docetaxel and doxorubicin in 2 clinical trials, approximately 75% of FN episodes occurred in the first cycle [45]. Again, in a multicenter, double-blind, placebo-controlled phase III study on prophylactic pegfilgrastim use in patients with metastatic breast cancer receiving docetaxel, 67% of all FN events in the initial placebo group occurred in the first cycle of chemotherapy [32, 34]. Given the high frequency of first-cycle FN, waiting until a neutropenic complication occurs before implementing supportive measures will result in a situation where most of the complications to be prevented have already occurred. Consequently, G-CSF administration from the first chemotherapy cycle onwards is needed to significantly reduce the incidence of FN necessitating hospitalization and i.v. antibiotics. However, even in patients who experienced FN in the first cycle, delivery of full-dose therapy on schedule is possible with secondary G-CSF prophylaxis [32].

More recent efforts to improve the decision-making process have focused on developing evidence-based clinical prediction or risk models. Such models may help to identify patients who are most likely to experience neutropenic complications, including FN, in order to use preventive strategies, such as prophylactic CSFs, more cost-effectively. Silber et al. [46] developed and retrospectively validated a model predicting patient risk for FN, severe neutropenia and dose reduction or delay of chemotherapy based on the first-cycle absolute neutrophil count (ANC) nadir in women treated with adjuvant chemotherapy for early-stage breast cancer. The authors

Table 2. International recommendations for primary prophylactic CSF administration [13, 57]

Circum-stances	ASCO Guidelines for Primary Prophylactic CSF Administration – version 07/2000	NCCN Practice Guidelines for CSF Administration in Oncology – version 02/2005
General	Based on cost-benefit analysis, primary G-CSFs administration is recommended for chemotherapy regimens with an expected FN rate of ≥ 40%.	Based on new data from clinical trials and economic models, routine G-CSF prophylaxis is recommended for chemotherapy regimens with a high risk of FN (> 20%).
Special	Primary G-CSF administration may be exceptionally warranted in patients at higher risk for chemotherapy-induced FN. Such risk factors might include the following: pre-existing neutropenia due to disease, extensive prior chemotherapy or previous irradiation to the pelvis or other areas containing large amounts of bone marrow, a history of recurrent FN while receiving earlier chemotherapy of similar or lesser close-intensity or conditions potentially enhancing the risk of serious infection, e.g. poor performance status and more advanced cancer, decreased immune function (e.g. HIV), open wounds or already-active tissue infections. It is anticipated that, depending on the unique features of the clinical situation, there will be instances when the administration of a G-CSF will be recommended.	For chemotherapy regimens with an intermediate risk of FN (10–20%), individual patient risk factors that can increase the risk for development of FN, should be evaluated. Such risk factors include the following: previous history of severe neutropenia with similar chemotherapy, extensive prior chemotherapy, concurrent or prior radiation therapy to marrow containing bone, preexisting neutropenia (< 1,000/ml) or lymphocytopenia, age (> 65 years), poor performance status (ECOG 2), poor nutritional status (e.g. low albumin), decreased immune function, bone marrow involvement with tumor, advanced or uncontrolled cancer, open wounds, active tissue infection, COPD, cardiovascular disease, liver disease (elevated bilirubin, alkaline phosphatase), diabetes mellitus, low baseline hemoglobin.

demonstrated that using this model, patients can be ranked with a high level of certainty and good degree of discrimination between high-risk group (first-cycle ANC nadir $< 0.25 \times 10^9$/l) and low-risk group (first-cycle ANC nadir $> 0.25 \times 10^9$/l) for the development of severe neutropenia and its complications. Studies analyzing additional chemotherapy regimens have since confirmed the value of the first-cycle ANC nadir as a predictor of neutropenic complications in patients receiving adjuvant chemotherapy for early-stage breast cancer [6]. The value of the first-cycle ANC nadir in identifying patients at high risk of neutropenic complications was also confirmed in a large prospective study of patients with early-stage breast cancer [47].

Based on the available clinical data, the National Comprehensive Cancer Network (NCCN) panel members recommend the routine use of G-CSFs (primary prophylaxis) for high-risk (> 20% FN rate) chemotherapy regimens in order to prevent development of FN in patients receiving treatment with curative intent, adjuvant therapy or treatment expected to prolong survival and improve quality of live. There is level 1 evidence for the use of G-CSFs with respect to the following endpoints: risk of FN, hospitalization, i.v. antibiotics and supportive dose-dense regimens. Both, retrospective and prospective studies, suggest that a decrease in dose intensity can compromise treatment outcome. Nevertheless, it has not yet been demonstrated that maintenance of the planned chemotherapy dose using G-CSFs provides DFS or OS benefits [2, 13, 23, 48]. Among the chemotherapy regimens with a FN incidence of > 20% (table 1) in clinical trials with chemotherapy-naive patients and therefore considered by the NCCN panel as high-risk, are such regimens as AC→T (doxorubicin, cyclophosphamide, docetaxel), AT (doxorubicin, paclitaxel) and TAC (docetaxel, doxorubicin, cyclophosphamide) [40–51]. With intermediate-risk (10–20% FN rate) and low-risk regimens for FN development, such as docetaxel, AC and DX (docetaxel, capecitabine) [52–54], patient- and disease-specific risk factors that may impact on the FN risk need to be evaluated. As previously discussed, patient age (> 70 years) itself is a general risk factor for FN development. 3 studies showed that, in addition to age, poor performance status (WHOG > 1) and poor nutritional status (e.g. low albumin) are significant risk factors for chemotherapy-induced FN. Thus, in older patients, physiologic age or frailty may be a more accurate risk predictor than chronological age [55]. Comorbidities, such as liver disease (elevated bilirubin, alkaline phosphatase), kidney and heart disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, obesity and decreased immune function, increase the risk of severe neutropenia and FN. It was shown that comorbidities, such as COPD, pneumonia, obesity with a body surface area of > 2 m^2, cerebrovascular disease, cardiovascular disease, prior fungal infection, connective tissue disease and sepsis, increase the risk of serious complications from FN, including prolonged hospitalization and death [56, 57]. In addition, some laboratory abnormalities, such as low pre-treatment white blood cell counts and baseline hemoglobin (< 12 g/dl), have been identified as predictors for chemotherapy-induced severe neutropenia or FN in cycle 1 [3, 16]. For low-risk patients, defined by a FN risk of < 10%, routine use of G-CSFs is not recommended in any treatment setting. In this group of patients, evaluation should be performed with every cycle to determine the risk categorization and treatment intent [57].

Recommendations for Clinical G-CSF Use

With the advent of modern, more myelotoxic chemotherapy regimens in breast cancer, in particular in the potentially curative adjuvant setting, optimal use of G-CSFs has become increasingly important. Current international clinical guidelines follow different strategies with regard to primary and secondary prophylaxis of FN. Based on cost-effectiveness studies, the ASCO 2000 guidelines recommended G-CSFs only for patients with a 40% or higher risk of developing FN [13]. Similar recommendations have been provided by the ESMO 2005 guidelines [23], whereas the NCCN guidelines for use of myeloid growth factors advocate the prophylactic use of G-CSF in patients with a FN risk of > 20%. The NCCN panel even recommended the prophylactic use of G-CSF with chemotherapy regimens with an intermediate risk of FN (10–20%) if additional risk factors for development of FN are present (table 2). Similarly, the German AGO (German Working Group for Gynecologic Oncology) breast cancer therapy guidelines 2005 gave a strong (AGO ++) recommendation for primary prophylaxis with G-CSFs in patients receiving chemotherapy regimens associated with a > 20% FN rate as well as secondary prophylaxis (*www.ago-online.org*).

Based upon these national and international guidelines as well as the available clinical data, routine prophylactic use of G-CSFs can be recommended for breast cancer patients at a 20% or higher risk of FN while receiving treatment with curative intent or treatment expected to substantially prolong survival and improve quality of live. In the palliative setting, alternative approaches, such as dose reduction or use of a less myelotoxic chemotherapy regimen, need to be considered.

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