Clinical practice in secondary prophylaxis and management of febrile neutropenia in Poland: results of the febrile neutropenia awareness project

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Aim of the study: This paper presents the second part of the *GoPractice* project involving oncologists from seven Polish provinces. The aim of this part of the project was to assess the knowledge of oncologists on indications for granulocyte colony-stimulating factor (G-CSF) secondary prophylaxis (SP) of febrile neutropenia (FN) and FN management based on current therapeutic guidelines (Polish Society of Clinical Oncology [PTOK] and European Organisation for Research and Treatment of Cancer [EORTC]).

Material and methods: The project involved 169 oncologists from 7 regions working in large specialist oncological centers, university hospitals, regional and city hospitals, specialist outpatient clinics and oncological wards in small, local hospitals. The participants completed a questionnaire based on 7 prepared clinical cases of patients with different tumor types and patient characteristics, receiving chemotherapy (CT) with different levels of FN risk. Participants answered questions related to FN risk assessment and G-CSF use as secondary prophylaxis (SP) and for the management of FN. After completing the questionnaire, the participants proceeded to an educational module in which they were provided with an analysis of correct diagnostic and therapeutic procedures according to the PTOK and EORTC guidelines.

Results and Conclusions: Indications for G-CSF SP were generally well recognized: in nearly 90% of responses, oncologists assessed correctly indications/lack of indications for secondary prophylaxis, in accordance with guideline recommendations and Experts' opinion. However, the use of daily G-CSFs was often recommended by the study participants for the management of FN. This clinical practice is contradictory to PTOK and EORTC recommendations and may unnecessarily increase treatment costs. Changing this clinical approach may be achieved through regular training to improve guideline adherence.

Key words: chemotherapy induced neutropenia, G-CSF, febrile neutropenia prophylaxis.

Contemp Oncol (Pozn) 2014; 18 (6): 425–428
DOI: 10.5114/wo.2014.47905

Introduction

According to the guidelines of the Polish Society of Clinical Oncology (PTOK) and the European Organisation for Research and Treatment of Cancer (EORTC), routine implementation of primary prophylaxis (PP) with G-CSF is recommended for patients receiving chemotherapy in which the overall risk of febrile neutropenia (FN) exceeds 20%. In the remaining patients with a lower risk of FN, the use of G-CSF in PP, that is, beginning in the first cycle of chemotherapy (CT), is not recommended. When severe neutropenia or FN may compromise clinical outcomes, secondary prophylaxis (SP) of FN is recommended in the cycles following the FN or severe neutropenia event. An alternative intervention is drug dose reduction or switching to a less toxic chemotherapy regimen. Patient management largely depends on the treatment intention, as lowering dose intensity, especially in curative treatment plans, may greatly impair therapy effectiveness [1–5]. Secondary prophylaxis of FN involves G-CSF administration with either a daily G-CSF or with once-per-cycle pegfilgrastim. According to PTOK guidelines, G-CSF should be given 24–72 hours after chemotherapy as a single subcutaneous injection (pegfilgrastim) or for a period longer than 5 days (daily G-CSF).

The most important recommendation for the treatment of FN is the administration of a wide range antibiotic [6, 7] and control of the neutrophil count. In cases of suspected fungal or viral infections, administration of antiviral (acyclovir) and antifungal drugs is recommended, as well as further microbiological diagnostics, if necessary. Management of existing FN with G-CSF is not recommended except in situations where: there is no evidence of a response to antibiotic therapy; serious and potentially fatal infection or complications are possible; FN is diagnosed despite the use of prophylactic non-pegylated growth factors; or there are other factors that increase the risk of complications [6, 7].

Material and methods

The results presented in this paper were obtained from the first part of the *GoPractice* project described in the same issue of the journal. In this second part of the project, participants answered questions regarding:

1. *Assessment of indications for G-CSF SP and method of G-CSF administration*. Participants were asked to assess clinical cases and determine whether they would recommend G-CSF SP in the CT cycle following FN. The answers of participants were considered correct in the context of the guidelines if G-CSF SP was recommended in patients where treatment intent was curative; other answers considered correct included reduction in CT dose intensity in cases of palliative care or switching to a lower-risk CT regimen.
2. *Secondary prophylaxis method*. Participants selected the choice of G-CSF type and the method of administration and dosing.
3. *Management of febrile neutropenia*. Participants were asked to provide their recommendation for how to treat FN. The available options were to give antibiotics without concurrent G-CSF or to give antibiotics accompanied by daily G-CSF treatment. The correct answers were those consistent with PTOK and EORTC recommendations.

Results

Risk assessment

In nearly 90% of responses, oncologists assessed indications/lack of indications for secondary prophylaxis in accordance with guideline recommendations and the Experts' opinion (Fig. 1).

Assessment of indications for secondary prophylaxis with G-CSF and method of SP administration

Less frequent use of SP was declared in palliative cases (breast cancer), recommending instead a dose reduction or a delay of the next cycle of chemotherapy (Fig. 2).

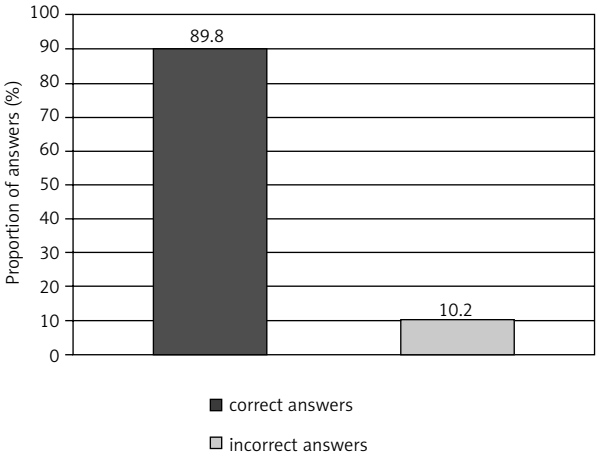


Fig. 1. Percentage of correct and incorrect answers to the question "Would you recommend secondary prophylaxis with G-CSF in the CT cycle following FN in this case?" – summary of answers for all cases

Secondary prophylaxis method

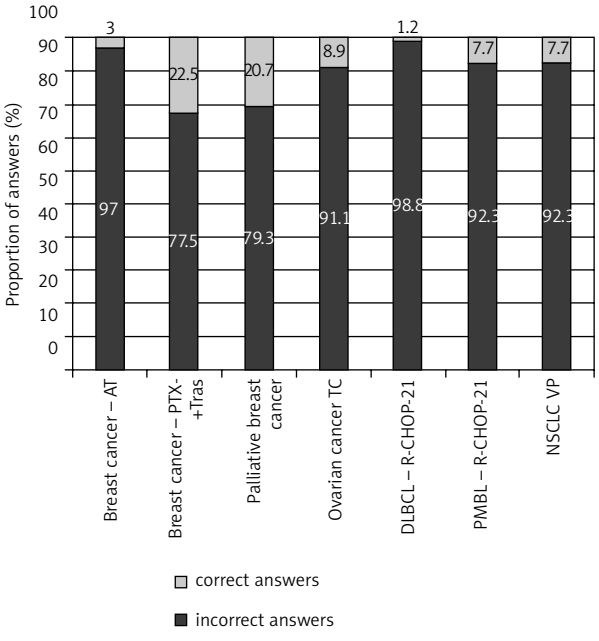
When administration of G-CSF SP was selected, administration of pegfilgrastim or daily G-CSF for a period longer than five days was recommended in 86% of responses. Only 14% of answers selected G-CSF administration for a period shorter than 5 days.

Management of febrile neutropenia

The answers to the question concerning the management of FN are presented in Figure 3. Nearly half of the answers overall (48%) were consistent with PTOK guidelines, recommending the use of antibiotics and control of the neutrophil count. However, the remainder of the answers (52%) recommended giving antibiotic therapy accompanied by the use of short-acting G-CSF, which appears to contradict the current PTOK and EORTC recommendations and Experts' opinion.

Discussion

The occurrence of FN in one cycle increases the risk of FN events in subsequent cycles. To reduce the risk of this complication in patients who have not received prophylactic G-CSF, it is recommended to give G-CSF as SP or, in the case of palliative patients where the treatment aims at improving their quality of life, it is advisable to reduce or delay the next chemotherapy dose or to replace the CT regimen with a less toxic one. In the case of CT-induced FN in patients not receiving palliative treatment, some of



AT – doxorubicin, docetaxel; PTX + Tras – paclitaxel + trastuzumab; TC – paclitaxel, carboplatin; DLBCL – diffuse large B-cell lymphoma; R-CHOP-21 – rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; PMBL – primary mediastinal B-cell lymphoma; NSCLC – non-small-cell lung cancer; VP – vinorelbine, cisplatin

Fig. 2. Secondary prophylaxis – correct and incorrect answers to the question: "Would you recommend secondary prophylaxis with G-CSF in the CT cycle following FN in this situation?" for different cases

the participants, instead of administering SP with G-CSF as recommended, answered that they would apply a dose reduction or delay of CT in the next cycle. Reducing the dose intensity of chemotherapy may compromise survival outcomes in the curative setting [2].

The current standards of FN treatment differ depending on the risk of subsequent complications, including death. Patients with FN frequently require hospitalization, but in some cases outpatient clinic-based treatment may be an acceptable option [6]. The PTOK guidelines refer to the Multinational Association for Supportive Care (MASCC) index that allows the clinicians to make a quick assessment of the risk of complications [15]. The MASCC index is a 26-point scale, and the patients with a score of ≥ 21 are considered to have a low risk of FN-associated complications. Consequently, the National Comprehensive Cancer Network (NCCN) recommends hospitalization in patients with a MASCC score of ≤ 21 or if at least one of the following conditions is met: FN during hospitalization, serious comorbidities or unstable patient condition, expected duration of agranulocytosis (neutrophil count < 100/µl) is at least 7 days, signs of hepatic failure (AlAT or AspAT levels 5 times above the normal range), signs of renal failure (creatinine clearance < 30 ml/min), neoplastic disease progression or incomplete remission in acute leukemia patients, pneumonia or another clinically important infection, alemtuzumab therapy, mucosal inflammation of third or fourth degree.

The recommended therapeutic strategy in FN patients includes empirical administration of wide-range antibiotics targeted at the potentially most dangerous pathogens. The use of G-CSF for the management of FN and FN-related complications is not recommended [9], and unnecessarily increases overall therapy costs while providing no clinical benefit [8]. The only exceptions to this are situations with an increased risk of death and other disease, e.g. sepsis, tissue infections or prolonged neutropenia. Growth factors should be particularly avoided in patients with infections not associated with neutropenia, such as nosocomial pneumonia.

Febrile neutropenia not only is a major risk factor for compromising therapy effectiveness (as a result of a reduction or delay of the next CT dose) but also greatly increases the cost and frequency of cancer patients' hospitalization [10]. Numerous studies analyzing the cost of cancer treatment have revealed that FN management was expensive, as it usually required a hospital stay. Based on US data from hospital discharge databases covering more than 40,000 patients treated for cancer in the years 1995–2000, it was found that a single episode of FN required an average of 11.5 days of hospitalization, incurring an average cost of 19,000 dollars. Hospitalizations lasting longer than 10 days accounted for 78% of the total costs, with risk factors such as various types of infection, including fungal infections. In a paper based on Canadian data, the authors calculated that the average duration of hospitalization of an FN patient was 6.8 days and the average cost of one intervention was over 6,000 Canadian dollars [11]. The authors believe that an economic analysis of the treatment costs may result in a better assessment of FN risk and the development of alternative FN management strategies, such as outpatient treatment or shortened hospitalization. The possibility of outpatient treatment of febrile neutropenia was evaluated in 2,131 patients who experienced 458 FN events [12]. The researchers concluded that outpatient treatment was possible only in patients with a low risk of complications of FN, and that the hospitalization costs in those cases were lower due to shorter hospital stays and a smaller amount of administered drugs. A retrospective US study involving more than 16,000 cancer patients hospitalized for FN confirmed high costs of treatment and a high risk of FN-related death. Significant differences in the costs of FN treatment were found depending on the type of cancer, comorbidities and type of infection. The highest mortality rate was found among patients with lung cancer (15.7%), and the longest hospitalization and highest costs were recorded in lymphoma patients [13].

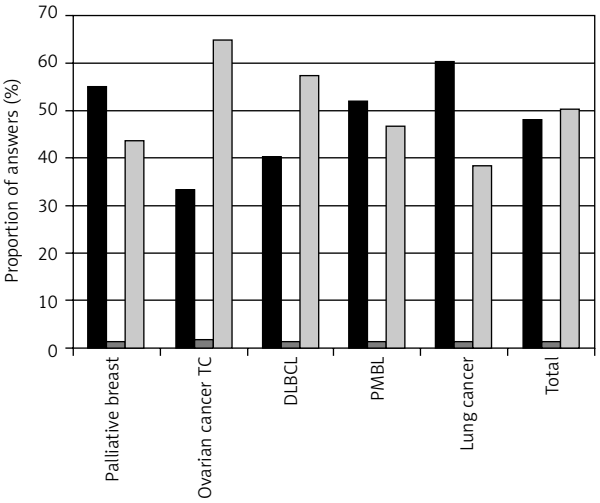


Fig. 3. Answers to the question: "How would you proceed in this situation (febrile neutropenia)?"

The responses of participants to administer G-CSF for the treatment of FN was the most common inconsistency with the national and international guidelines (PTOK and EORTC). However, since treating FN with G-CSFs seems to be a fairly common clinical practice, Wright *et al.* [14] published the results of a project in which they assessed the compliance of FN treatment in patients with solid tumors to available therapeutic guidelines. Although 79% of patients were prescribed antibiotic therapy, as indicated in the guidelines, 37% of individuals were unnecessarily given vancomycin and 63% received a G-CSF. During a 10-year study period, vancomycin consumption increased by 38% and G-CSF decreased by 18%. Patients treated at high FN-volume hospitals and by hospitalists specializing

in the field were more likely to receive guideline-based treatment. It was also found that rapid implementation of recommended antibiotics in patients with a low risk of FN reduced the hospitalization frequency.

In conclusion, it seems that although G-CSF SP is correctly administered, the management of FN may be further improved, as the rate of non-compliance with the guidelines was around 50%. The key issue seems to be an incorrect use of G-CSFs in the treatment of FN as a routine clinical practice. Improved identification of high-risk patients and administering appropriate PP to them can reduce the FN events, the G-CSF use for FN treatment and SP use in the subsequent cycles. The change of this clinical approach may be achieved through regular training sessions that would help oncologists re-consider their treatment recommendations, and also align with the most current treatment guidelines. The training should also highlight the need for an individualized approach to FN management, based on the MASCC score and PTOK recommendations.

The GoPractice project was supported by Amgen Biotechnologia Sp. z o.o. Editorial assistance was provided by James O'Kelly, an employee of Amgen Ltd.

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Submitted: 23.10.2014
Accepted: 20.11.2014