Primary or secondary G-CSF prophylaxis to support TAC chemotherapy in breast cancer?

Taxanes and anthracyclines are two of the most active agents against breast cancer. Many trials with a positive outcome have recently been reported in the adjuvant setting.

In the Cancer and Leukaemia Group B (CALGB) 9344 trial, 3121 women with node-positive breast cancer were randomly assigned to receive a combination of four cycles of AC (doxorubicin 60, 75 or 90 mg/m² and cyclophosphamide), followed by either no further therapy or four cycles of paclitaxel (Taxol) [1]. The addition of paclitaxel improved both 5-year disease-free survival (DFS) (70% versus 65%) and overall survival (OS) (80% versus 77%). In the NSABP B-28 trial, with a comparable design in 3060 women with node-positive breast cancer, the addition of paclitaxel resulted in significant improvement in 5-year DFS (76% versus 72%), although no improvement in OS was seen [2]. In the BCRG 001 study, TAC (docetaxel, adriamycin, cyclophosphamide) outperformed classical FAC (5-fluorouracil, adriamycin, cyclophosphamide) with a 5-year DFS difference (75% versus 68%) and an OS difference (87% versus 81%) [3]. In the French PACS 01 trial, in 1999, of women with node-positive breast cancer, the addition of three cycles of docetaxel after three cycles of i.v. FEC (5-fluorouracil, epirubicin, cyclophosphamide) compared with six cycles of FEC resulted in a significant DFS benefit (78% versus 73%) and OS benefit (91% versus 87%) [4]. A U.S. Oncology trial compared outcome of four cycles of TC (docetaxel, cyclophosphamide) with four cycles of AC in women with node-negative or node-positive breast cancer and reported a significant 5-year difference in DFS (86% versus 80%), but no difference in OS [5]. At American Society of Clinical Oncology (ASCO) 2006, the first results of the BIG 2-98 at 5-year median follow-up were presented [6]. Docetaxel was given concurrently or sequentially to anthracycline-based adjuvant therapy in patients with node-positive breast cancer in comparison to a non-docetaxel regimen. Addition of docetaxel resulted in improved event-free survival which was of borderline significance, with the sequential approach being superior to the concurrent schedule. The first results of the Taxit 216 study were also presented at ASCO 2006 [7]. In total, 997 patients with node-positive breast cancer were included. The sequential addition of docetaxel to epirubicin and cyclophosphamide, methotrexate, 5-fluorouracil or high-dose cyclophosphamide resulted in a borderline significant improvement in DFS and OS.

In conclusion, on the basis of the available data with many positive and few negative trials, one can consider the use of taxanes to be a standard of care in the adjuvant setting in node-positive breast cancer, although the preferred schedule, concurrent or sequential, with or without dose densification, needs to be clarified from ongoing trials. Obviously, it is important to determine who will benefit the most from taxanes.

In the CALGB 9344 trial, the hazard ratio of AC plus paclitaxel versus AC alone was 0.72 for those with estrogen receptor (ER)-negative tumors but only 0.91 for patients with ER-positive tumors, almost all of whom received adjuvant tamoxifen [1]. This was in contrast to a subset analysis in the NSABP B-28 trial where the effect of paclitaxel according to hormone receptor status did not reveal significant interactions [2]. In another unplanned subset analysis, it was reported that the HER2/neu status was predictive for the impact of paclitaxel on DFS in the CALGB 9344 trial [8]. Of note, in the aforementioned trials, predominantly patients with node-positive breast cancer were included. The absolute benefit in patients with node-negative disease may be much smaller and this may not outweigh the expected increase in toxicity. With this in mind, it is important to perform studies on reducing toxicity from taxane-containing regimens.

In this issue of the *Annals of Oncology*, Martin et al. [9] report on the results of a randomized adjuvant trial comparing TAC with FAC for high-risk N0 breast cancer patients, the GEICAM 9805 trial. Comparisons are reported for toxicity and quality of life, not for efficacy, as follow-up time is still too short. After a protocol amendment, patients on the TAC arm received primary granulocyte colony-stimulating factor (G-CSF) prophylaxis, whereas before the amendment, only secondary G-CSF prophylaxis was allowed or even mandatory after an episode of febrile neutropenia. In addition, all TAC patients received primary ciprofloxacin prophylaxis. So, in addition to the upfront planned comparison of TAC versus FAC, the unplanned comparison of TAC-pre versus TAC-post amendment is reported. The authors consider the comparison to be reliable, though not randomized, since patient characteristics and treatment apart from G-CSF prophylaxis were homogeneous during the study. This comparison is very interesting, as it is to our knowledge the first ever reported of primary versus secondary G-CSF prophylaxis.

In this GEICAM 9805 study, the use of ‘primary’ G-CSF prophylaxis significantly reduced the incidence of febrile neutropenia associated with TAC chemotherapy. The percentage of patients who had febrile neutropenia in one or more cycles according to protocol definition, which was slightly different from NCI-CTC criteria, was 24.6% and 6.5% in TAC-pre and TAC-post groups, respectively. Of note, in the TAC-pre group, 71.1% of patients had received ‘secondary’ G-CSF prophylaxis during, on average, four cycles of

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Febrile neutropenia is a major threat to patients treated with chemotherapy. It can result in death, increased hospitalizations and i.v. antibiotic use. In addition, it can lead to significant chemotherapy dose modifications, which may theoretically be of concern for treatments with curative intent. On the other hand, most of the recently European Organisation for Research and Treatment of Cancer-reviewed evidence indicates that primary and secondary G-CSF prophylaxis had no significant impact on survival, despite the fact that G-CSF prophylaxis enabled the maintenance of chemotherapy dose and dose intensity [10]. In the GEICAM 9805 study, primary G-CSF support did not lead to improved median dose intensity or cumulative dose when compared with secondary G-CSF prophylaxis, although the percentage of patients who completed six cycles of therapy increased significantly [9]. In any case, prophylactic strategies may be supportive for regimens with increased risk of febrile neutropenia. For this purpose, prophylactic G-CSF and prophylactic antibiotics have successfully been applied [11–13]. The use of the hematopoietic growth factor G-CSF was shown to shorten the duration of neutropenia, resulting in the reduction of the incidence of febrile neutropenia, hospitalization and use of i.v. therapeutic antibiotics by ~50% [11]. The new European and the recently updated guideline of the ASCO recommend the use of primary growth factors when the risk of febrile neutropenia is ~20% and no other equally effective regimen that does not require growth factors is available [10, 14].

In the BCIRG 001 trial, with the use of TAC as adjuvant treatment in node-positive breast cancer, primary G-CSF prophylaxis was not permitted, whereas secondary G-CSF prophylaxis was mandatory [3]. Moreover, all patients received primary prophylactic ciprofloxacin 500 mg b.i.d. on days 5–14 of each cycle. Febrile neutropenia was observed in 24.7% of the patients in the TAC group and 2.5% of those in the FAC group, results which are quite similar to those observed in the comparable arms of the GEICAM 9805 trial.

In the BCIRG 004 trial on TAC chemotherapy in advanced breast cancer, it was shown that primary G-CSF prophylaxis reduced the incidence of febrile neutropenia to 7% of patients [15]. In the control arms with daily or alternate-day leristidim, a compound that induces multilineage hematopoietic recovery, the incidence of febrile neutropenia was 19% and 22%, respectively. Prophylactic antibiotics were not permitted. Of those developing febrile neutropenia, 65% of patients treated with alternate-day leristidim did so during the first cycle, as did 56% of those receiving daily leristidim and 50% of those treated with G-CSF.

Von Minckwitz reported the febrile neutropenic rates in the GEPARTRIO study, a phase III trial on the use of six to eight cycles of TAC as neoadjuvant treatment in primary breast cancer [16]. The first cohort received primary prophylactic filgrastim on days 3–12 (n = 390 patients), the second cohort received pegfilgrastim on day 2 after amendment 1 (n = 323 patients) and in the third cohort pegfilgrastim was combined with prophylactic ciprofloxacin (n = 236). Febrile neutropenia was reported in 17% versus 6% versus 4% of patients, respectively, for the three cohorts (P < 0.0001). The delayed start of filgrastim (on day 3 instead of on day 2) may explain the relative high-febrile neutropenia incidence in the first cohort.

Brain et al. [17] reported on the results of the RAPP-01 trial of doxorubicin plus docetaxel for intermediate-risk breast cancer. Chemotherapy was delivered without primary G-CSF prophylaxis. Use of G-CSF was recommended only for grade 3 or 4 febrile neutropenia. Three cases of life-threatening sepsis were described, of which two occurred during the first chemotherapy cycle, both with a fatal outcome.

So, it is well conceived that doxorubicin–docetaxel-containing regimens are associated with a high incidence of febrile neutropenia. Secondary G-CSF prophylaxis cannot reduce the incidence of febrile neutropenia to an acceptable degree. It is important to stress that so far there are no studies prospectively carried out on the value of secondary G-CSF prophylaxis. The pivotal G-CSF registration trial allowed patients in the placebo arm to receive open-label G-CSF in subsequent cycles of chemotherapy after febrile neutropenia in the first cycle [11]. This resulted in a reduction in the rate of febrile neutropenia from 100% in the first cycle to 23% in the second cycle. However, as many trials report a decline in the incidence of febrile neutropenia in later cycles without administering prophylaxis, no definite conclusions on the efficacy of secondary prophylaxis can be drawn from these observations. In fact, our research group demonstrated that there is a higher baseline risk of febrile neutropenia for the first chemotherapy cycle compared with subsequent cycles in small-cell lung cancer patients [12, 13]. Also in advanced breast cancer, the majority of first-observed episodes of febrile neutropenia occur in the initial chemotherapy cycles [9, 15]. With primary G-CSF prophylaxis, the absolute neutrophil count nadir is less deep and of shorter duration in later cycles compared with the first cycle. This may suggest that there may be a priming effect of G-CSF to subsequent cycles, emphasizing that administration of G-CSF early in the course of treatment might be important [18, 19].

Another issue is the use of prophylactic antibiotics. Prophylactic antibiotics do not influence the severity of neutropenia, but may be effective as most infections are assumed to be caused by pathogens derived from the gastrointestinal tract. In a recently published meta-analysis, antibiotic prophylaxis was shown to significantly reduce the incidence of febrile neutropenia with a relative risk of infection-related mortality of 0.58 when compared with placebo or no intervention [20]. Further, it was demonstrated that prophylaxis with quinolones more effectively reduced mortality as compared with other antibiotics.

Of the discussed trials, the RAPP-01 trial is the only trial without any primary prophylaxis (no G-CSF and no antibiotic prophylaxis during the first chemotherapy cycle). In this study, the incidence of febrile neutropenia was extremely high, 40.8% in the doxorubicin–docetaxel group (versus 7.1% in the doxorubicin–cyclophosphamide group). All the other trials included at least primary ciprofloxacin prophylaxis. In the GEPARTRIO study with the cohort having combined primary prophylaxis by both pegfilgrastim and ciprofloxacin, the incidence of febrile neutropenia was the lowest [16].

In summary, taxanes have shown to improve the outcome in node-positive breast cancer. Translational research may
indicate which group of patients may benefit the most from the taxanes. Updated results from the GEICAM 9805 may shed further light on its value in node-negative breast cancer. Overall, TAC leads to more hematological and non-hematological toxic effects compared with FAC [3, 9]. Patient’s quality of life decreases during chemotherapy more with TAC than FAC, but returns to baseline values quickly thereafter [9]. In this issue of the Annals of Oncology, the value of primary compared with secondary G-CSF prophylaxis is highlighted, as it is well known that TAC chemotherapy is accompanied with increased risk of febrile neutropenia. The routine use of primary G-CSF prophylaxis is recommended on the basis of these new data, building on the evidence from previous reports on this topic. The role of prophylactic antibiotics is less well defined, and because of concern of emerging resistance it may be withheld in patients who have otherwise no additional risk factors, like old age, of febrile neutropenia.

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