Cyclooxygenase inhibitors may be more effective in hormone-dependent endometrial cancers: interaction between cyclooxygenase and aromatase

We read with great interest the article by Toyoki et al. [1]. They found a positive association between vascular endothelial growth factor (VEGF) and cyclooxygenase-2 (cox-2) on angiogenesis at an early stage in the growth of uterine endometrial cancer. They suggested that long-term administration of cox-2 inhibitors might be effective in the suppression of recurrent initiation of uterine endometrial cancers after curative resection. Currently, in vivo and in vitro studies on the uterine effects of aromatase inhibitors are limited. It is well known that some endometrial cancers are hormonally dependent. Since most of uterine endometrial cancers are postmenopausal, a principal source of circulating estrogen in these patients is from the conversion of adrenal androstenedione by aromatase. In addition to peripheral aromatization, aromatase is also elevated in endometrial cancer stroma [2]. Morales et al. [3], in the same issue of Annals of Oncology, also showed that third-generation aromatase inhibitors may prevent endometrial growth and reverse tamoxifen-induced uterine changes in postmenopausal breast cancer patients.

Furthermore, even though there was no direct data about the association between aromatase and cox in uterine endometrial cells, it has been shown that increased secretion of prostaglandins, such as prostaglandin E2 from constitutive cox-1 and inducible cox-2 isozymes present in epithelial and stromal cell compartments, will result in both autocrine and paracrine actions to increase aromatase expression in normal and malignant breast cells [4]. In the light of above information, cox-2 inhibitors may be more effective in hormone-dependent uterine endometrial cancers by further suppressing aromatase activity. In vitro and in vivo studies on uterine endometrial cancers are warranted to support our hypothesis.

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In vivo chemosensitivity-adapted preoperative chemotherapy in patients with early-stage breast cancer

In the January issue of Annals of Oncology, von Minckwitz and colleagues reported their pilot study of preoperative chemotherapy with the TAC regimen (docetaxel, adriamycin,
and cyclophosphamide) adapted by clinical evaluation after two cycles [1]. The patients with at least partial response received four additional cycles of TAC although the others were randomised to either TAC or the combination of vinorelbine and capecitabine (NX). A high complete pathological response rate (pCR) of 22.9% was obtained in responders to the first two cycles. Nevertheless, this study deserves a number of additional comments. The first point is the method of evaluation of response since there is also a demonstration of the poor correlation between palpation and echography. A second point is the recruitment which did not favour chemosensitivity given the minority of patients (36%) with histologic grade III, or with hormone negative status (32%). More than 25% of the patients were older than 60 years who would probably have poorly tolerated such a heavy regimen. We do not agree with the relatively optimistic presentation of the toxicity which included febrile neutropenia in 13.5% of the patients under TAC and grade III/IV neutropenia in 34% under NX. It must be taken into account that the patients have been particularly well followed in the setting of a clinical trial conducted in university hospitals. Moreover, the patients have been inevitably selected. These phenomenon are particularly well illustrated by the extremely low rate of manageable toxicity such as nausea, edema, or hand-foot syndrome. The administration of TAC or NX might be more problematic in general practice. Regarding the results, the low pCR after NX indicates the inefficacy of this regimen after failure of TAC, which is conceptually comprehensible and should lead to its disqualification. In fact, the key-point is the choice of TAC since a high proportion of the tumours is resistant to at least one of the three drugs while all patients are exposed to toxicity. There is a contradiction between in vivo adaptation and the use of a wide-spectrum regimen with no possibility of second-line therapy. In the Aberdeen study, the patients who were refractory to the anthracyclin-based regimen exceptionally took benefit from docetaxel [2]. In fact, all these studies indicates that there is a fraction of clearly refractory patients. Even an intensified regimen did not show improvement in the results. In a study of 57 patients with stage III disease receiving three cycles of epirubicin, 100 mg/m², and cyclophosphamide, 1200 mg/m² every two weeks, the pCR was only 3.5% [3]. A phase III study comparing EC (epirubicin, 120 mg/m² and cyclophosphamide, 830 mg/m² every 2 weeks) with FEC (5-fluorouracil, epirubicin, 60 mg/m² D1, and cyclophosphamide, 75 mg/m²/day D1-D14, one cycle every 4 weeks), resulted in equivalent pCR [4]. In conclusion, a sequential treatment including a taxane in responders seems an appropriate approach in hormone negative receptor patients with probably no loss of chance but less toxicity. Unfortunately, no alternative approach is proposed to the other patients while hormonal therapy, trastuzumab, or even irradiation might be considered.

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In vivo chemosensitivity adapted neoadjuvant chemotherapy in patients with early stage breast cancer: the Gepartrio pilot study

The Gepartrio pilot study undertaken by the German breast group (GBG) involved 269 patients and evaluated the possibility of the TAC regimen (docetaxel, Adriamycin, cyclophosphamide) as neoadjuvant therapy and randomized the non-responding patients to either continue with the same regimen or change to a non-cross-resistant treatment with NX (vinorelbine, capecitabine).

For the phase III trial, based on the results of the pilot trial, sonographic evaluation of response after two cycles of TAC was chosen instead of clinical evaluation and patients with only favorable prognostic factors were excluded (T2, ER/PR positive, G2, N0, >35 years). In addition, the hypothesis that a longer treatment might enhance the pCR rate is incorporated in the responder arm testing six versus eight cycles of TAC. As NX could not significantly improve the pCR in non-responding patients but showed a better toxicity profile than TAC, a non-inferiority design has been chosen for the phase III trial in that subset of patients.

Recruitment and treatment of the patients was not only carried out in university hospitals, which is clearly stated in the list of authors. The patients were not selected and the administration of TAC and NX was manageable in the outpatient setting of university hospitals as well as general or district hospitals. Because of the high rate of febrile neutropenia in the TAC arm with antibiotic prophylaxis only, the phase III trial included (pegylated)-GSF prophylaxis [1].