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Gonadotropin-releasing hormone analogs for ovarian function protection during chemotherapy in young early breast cancer patients: the last piece of the puzzle?

In western countries, nearly 6% of women with newly diagnosed breast cancer are younger than 40 years old [1]. This percentage rises to 25% in developing countries [2]. At least half of young women with breast cancer desire children after treatment [3]. Nevertheless, breast cancer patients have the lowest chances among cancer survivors to subsequently become pregnant [4]. A potential important cause of such a low pregnancy rate in breast cancer survivors is represented by the possible gonadal damage induced by anticancer systemic therapies [5]. At the time of treatment decision-making, ~50% of young breast cancer patients are concerned about the potential risk of developing chemotherapy-induced premature ovarian failure (POF) and subsequent fertility impairment [6]. Embryo or oocyte cryopreservation is considered standard fertility preserving techniques but they cannot protect gonadal function during chemotherapy [4, 7]. Temporary ovarian suppression with gonadotropin-releasing hormone analogs (GnRHa) during chemotherapy is another available option that has been mainly investigated as a strategy to preserve ovarian function during systemic cytotoxic therapy [5]. However, this strategy has been widely debated in the last years with supporters [8] and strong detractors [9] of its protective role.

The OPTION study, published in this issue of *Annals of Oncology*, provides additional insights on the efficacy of GnRHa as a strategy to preserve ovarian function during chemotherapy [10]. In this phase III study, 227 premenopausal breast cancer patients were randomized to receive adjuvant or neo-adjuvant chemotherapy alone (control group) or with concurrent administration of the GnRHa goserelin for the whole duration of systemic cytotoxic therapy (experimental group). Primary analysis was carried out in 202 patients (89% of the population randomized in the study). The study showed that concurrent use of GnRHa during chemotherapy was associated with a reduced incidence of amenorrhea (defined as no menses between 12 and 24 months after randomization), from 38.3% in the control group to 22.1% in the experimental group ($P = 0.015$). The protective effect of the GnRHa goserelin was also confirmed by the secondary analysis in which a composite endpoint was used to define chemotherapy-induced POF, i.e. amenorrhea and follicle-stimulating hormone values above 25 IU/l. This analysis was conducted in 131 patients (58% of the population randomized in the study): the incidence of chemotherapy-induced POF was 34.8% in the control group when compared with 18.5% in the experimental group ($P = 0.048$). The protective effect was more prominent in patients aged $\leq$40 years: in this subgroup of women, the incidence of amenorrhea decreased from 25.4% to 10.0% ($P = 0.032$) and the incidence of chemotherapy-induced POF from 20.0% to 2.6% ($P = 0.038$) when GnRHa was added to chemotherapy. On the contrary, in patients older than 40 years the difference in the incidence of both amenorrhea and chemotherapy-induced POF between the control and experimental groups was not statistically significant. Although no standard definition of chemotherapy-induced POF exists so far, it has been recently proposed that anti-Mullerian hormone (AMH), a reliable hallmark of ovarian reserve, may become a biomarker of gonadotoxicity following the use of anticancer systemic therapies [11, 12]. Secondary results from the OPTION study showed a marked fall of AMH values after chemotherapy in both treatment arms with no difference between the control and experimental groups. Taking into account these findings, the authors concluded that the amount of ovarian function

preserved by the use of GnRHa may be relatively small. However, the limited number of patients with available AMH values (109 women at 24 months, 48% of the population randomized in the study) does limit the reliability of this analysis [10].

The results of the OPTION study showing a beneficial effect of temporary ovarian suppression with GnRHa during chemotherapy in preserving ovarian function are consistent with those of the other largest studies that have recently investigated the efficacy of this strategy in breast cancer patients [13–15]. Along the same direction, our updated meta-analysis including 12 randomized controlled trials that assessed the role of temporary ovarian suppression with GnRHa during chemotherapy in 1231 premenopausal breast cancer patients confirmed the protective effective of this strategy [16]. We observed that the concurrent use of GnRHa during chemotherapy was associated with more than 60% reduction in the risk of developing chemotherapy-induced POF (odds ratio [OR] 0.36, 95% confidence intervals [CI] 0.23–0.57, $P < 0.001$) [16]. If the results of the largest phase III studies, including those of the OPTION trial as well as the findings of our meta-analysis, consistently show the beneficial effect of temporary ovarian suppression with GnRHa during chemotherapy in ovarian function protection, why is its role still debated? Skepticism about this strategy primarily relies on the fact that the main outcome investigated in all the trials was not represented by long-term pregnancy rate but resumption of menses that may not be a good surrogate of fertility restoration. Nevertheless, including data coming from the recent largest studies [14, 15], our meta-analysis showed a higher pregnancy rate in women treated with GnRHa than in those who received chemotherapy alone (OR 1.83, 95% CI 1.02–3.28, $P = 0.041$) [16]. Therefore, although the numbers remain relatively small (33 vs. 19 women with a subsequent pregnancy), these data suggest the possible additional role of temporary ovarian suppression with GnRHa during chemotherapy as a strategy not only for ovarian function protection but also for fertility preservation. Although the difference was not statistically significant, more pregnancies were observed in patients receiving GnRHa when compared with those treated with chemotherapy alone also in the OPTION study (9 vs. 6 pregnancies) [10].

On the basis of the growing amount of evidence on the protective role of temporary ovarian suppression with GnRHa during chemotherapy, several guidelines have been recently updated to acknowledge the possibility of discussing this strategy with young breast cancer patients interested in preserving fertility and/or ovarian function [17–20]. The results of the OPTION study further strengthen this recommendation. Embryo or oocyte cryopreservation remains the first strategies to be proposed in patients willing to preserve fertility before starting anticancer systemic therapies. Temporary ovarian suppression with GnRHa during chemotherapy should now be considered another standard option that is not an alternative nor mutually exclusive with the surgical strategies. With the results of the OPTION study, has the puzzle on the protective role of temporary ovarian suppression with GnRHa during chemotherapy been completed? We believe that the answer should be 'yes'. Nevertheless, an individual patient-data meta-analysis of randomized controlled trials investigating the role of temporary ovarian suppression with GnRHa during chemotherapy in breast cancer patients is currently ongoing (PROSPERO registration number: CRD42014015638) [5]. Final results of this meta-analysis, expected for the end of 2017, are awaited to better identify those patients who are more likely to benefit from the use of this strategy.

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Whose side are you on?

Data on the prognostic and predictive values of primary tumor sidedness in metastatic colorectal cancer (mCRC) patients have, over the last year or so, been reported at oncology meetings and, in some cases, published subsequently as full articles. The present edition of *Annals of Oncology* includes two major articles, one on the impact of tumor sidedness in three panitumumab trials [1] and the other a meta-analysis of published and unpublished data from randomized controlled trials, comparing chemotherapy plus anti-epidermal growth factor receptors (EGFRs) with chemotherapy alone or combined with bevacizumab [2]. The vast majority of these trials deal with treatment-naive *RAS* wild-type mCRC patients, except for one in the meta-analysis which is testing chemotherapy plus or minus panitumumab in a second-line setting.

The German AIO Group was the first to address the question of the prognostic and predictive value of primary tumor sidedness using recent treatment schedules, and reported initial findings from the AIO KRK 0306 (FIRE-3) trial of first-line treatment with FOLFIRI in combination with cetuximab or bevacizumab [3]. Data from an analysis of FIRE-3 and CRYSTAL (a trial testing chemotherapy plus or minus cetuximab) have been then analyzed together and recently published [4]. The results published in this issue of *Annals of Oncology*, essentially mirror those of these previous works with cetuximab and therefore greatly strengthen the initially suggested prognostic and predictive values of primary tumor sidedness.

The first important result from these studies is that sidedness, which has for decades been recognized as a significant prognostic factor in mCRC [5], is still an important and clinically relevant prognostic factor in 2017 in the era of doublet chemotherapy associated with a targeted agent. Why patients with proximal tumors fare worse than those with distal tumors remains unclear. One may argue that it is because patients with proximal tumors are generally older, that the tumor is more often poorly differentiated, and that the primary tumor is less often removed in these patients. At the molecular level, *BRAF* mutations, the CpG island methylator phenotype (CIMP+), and the deficient mismatch repair phenotype (dMMR), which are known to be indicative of a poor prognosis in metastatic patients, are more often present in proximal tumors [6]. But multivariate analyses have shown that, even when adjusted for some of these factors [1], tumor sidedness remains prognostic, suggesting that these factors may only in part explain the poor prognosis of proximal tumors. Even if it seems a bit disappointing, at the time of consensual worldwide molecular classifications in CRC patients [7], we have to admit that tumor location and anatomy are relevant and may yield prognostic information in our daily practice, where molecular assessments are not always performed. So, tumor location and anatomy should henceforth be taken into account as a stratification factor for all future clinical trials in mCRC and in the years ahead, we will have to identify the "still unknown" factors that confer such a poor prognosis on proximal tumors.

The second important result is that proximal and distal tumors do not seem to respond in the same way to anti-EGFR and anti-vascular endothelial growth factor (VEGF) therapies. Current knowledge, enhanced by these two articles, suggests that first-line anti-EGFRs should be considered for distal mCRC and that anti-VEGF therapy may be more appropriate for proximal colon cancers. However, whereas the results are significant and quite robust for distal tumors and their excellent outcome with first-line anti-EGFRs, the results for proximal tumors are far less clear to date. This is due, at least in part, to the lower number of proximal tumors (one-third of the whole population), which limits statistical power and hence the ability to show any significant differences and also the reliability of other findings. For example, objective response rates remain in favor of anti-EGFRs even in the proximal tumor group and in trials with chemotherapy plus bevacizumab as the control arm, suggesting that at least some patients with proximal tumors may still benefit from anti-EGFRs. This suggests that rather than anti-EGFRs being ineffective in proximal tumor patients, the optimal treatment sequence in a continuum of care for these patients should not start with anti-EGFRs in most cases. As proximal tumors have a poor prognosis and are potentially more resistant to anti-EGFRs, a trial is probably needed to assess aggressive first-line treatment with a triplet chemotherapeutic regimen +/− a targeted agent, in patients