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The Role of Steroid Receptors and HER2 in Ovarian Cancer

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Ovarian cancer is one of the most lethal female malignancies. Despite of all the efforts in surgery and chemotherapy, advanced disease, which is the majority of the cases at the time of diagnosis, is associated with poor survival [1]. Besides, epithelial ovarian cancer (EOC) is a disease with great heterogeneity; so, the determination of individual tumor characteristics can be associated with different clinical behavior and may have impact on treatment and prognosis.

Tumor cells do interact with the environment around them [2]. In recent years, with the development of the molecular biology and immunologic methods, molecules such as the human epidermal growth factor receptor type 2 (HER2), and the steroid receptors, estrogen (ER), progesterone (PR) and androgen (AR), have been tested as potential biomarkers of individualized clinical behavior of cancer.

The effect of steroid hormones in carcinogenesis has been studied specially for breast and endometrial cancer with well-known and promising results for therapy. However for ovarian cancer these results have been conflicting and unclear [3,4]. While the expression of PR has been shown to predict better prognosis with apoptotic effect [5], a positive ER status has shown discrepant results [6-8]depending on the subtype of ER and tumor type [9]. In recurrent low-grade carcinoma of the ovary or peritoneum, hormonal therapies had a greater anti-tumor activity in ER+/PR+ patients than in ER+/PR- patients; although it was not statistical significant [10].The status of the AR and HER2 in ovarian cancer has also showed unclear results. Bookman and colleagues described a limited clinical value of trastuzumab in recurrent ovarian cancer because of the low frequency of HER2 overexpression [11-14]. Also at study, the subgroup of "triple negative epithelial ovarian cancer" (TNEOC), i.e., tumors that do not express ER (subtype alpha-ER), PR and HER2, may be significantly more aggressive and display a poorer prognosis than non-TNEOC tumors [15], similarly as evidenced in studies for breast cancer [16]. A recent review and meta-analysis of behavior found that PR predicted favorable survival, while HER2 expression had a negative effect on survival. ER expression remains controversial suggesting a protector effect especially of ERβ expression which data was limited by the sample size [17]. Although all this conflicting data is true to some extent it is important to emphasize that most ovarian cancer biomarker studies are not subtype specific and this can lead to misleading results [18]. In 2013, Sieh and colleagues published a collaborative study with 2933 women and analyzed hormonal-receptor expression by tumor subtype and ovarian cancer survival. They found that PR positivity was associated with disease-specific survival in endometrioid carcinoma and high-grade serous carcinoma and ER positivity was associated with disease-specific survival in endometrioid carcinoma. No significant associations were found for mucinous, clear-cell or low-grade serous carcinoma [19].

Recently our group published a study which analyzed the contribution of the expression of ER (α and β), PR, AR and HER2 and "triple-negative" tumor status to disease-free and overall survival in 152 women with epithelial ovarian cancer [20]. Our results showed that women with ERα positivity had a greater disease free-survival but had no effect on overall survival. However, this result was not subtype-specific and hormonal expression in these patients should be analyzed by tumor subtype as Sieh did for clearer results. The previous reported findings about TNEOC were not observed at our study, so those controversies still persist.

In conclusion, ovarian cancer subtypes are different diseases. These differences lead to heterogeneous responses to treatment. So, biomarker studies should be stratified by subtype to establish whether hormone-receptor status predicts behavior in EOC, and whether it could guide to personalised treatment for ovarian cancer, such as endocrine treatment.

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