Editorial Commentary

Adjuvant therapy of endometrial cancer: "taxane or not taxane, this is the question"

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Endometrial cancer is the fifth cause of cancer in women, with an incidence rate of more than 300,000 new cases per year worldwide (1). In USA it is the most common gynecologic malignancy, with approximately 61,880 newly diagnosed cases and 12,160 deaths expected in 2019 (2). Most cases are diagnosed at an early stage and have relatively good survival rates; however, women diagnosed with recurrent disease or advanced stages have a very poor prognosis (3). The standard treatment of endometrial carcinoma is hysterectomy plus bilateral salpingo-oophorectomy. After surgical treatment, patients with low risk early stage receive only adjuvant radiation, whereas chemotherapy +/– radiotherapy is given to high risk early stages, locally advanced disease not amenable of surgery, or to those patients with residual disease. Almost 75% of endometrial cancers are diagnosed at an early stage (FIGO stage I or II): for these patients the 5-year overall survival ranges from 74% to 91%; for patients with FIGO stage III, the 5-year overall survival is 57–66%, whereas for stage IV disease is only 20–26%. Lymph node metastatic involvement is a critical prognostic factor for disease free survival. In fact, for those patients without lymph node metastasis, 5-year disease free survival is about 90%, 60–70% in patients with involvement of pelvic lymph nodes, and 30–40% for those with paraaortic lymph node metastasis, respectively (4,5). In patients with advanced endometrial cancer, chemotherapy is still the mainstay of treatment, because targeted therapy as well as immunotherapy, have not yet demonstrated any utility. The standard chemotherapy for advanced disease is the combination of cisplatin plus doxorubicin that demonstrated improved response rates and PFS (5.7 *vs.* 3.8 months) compared with doxorubicin alone in a phase 3 study, although OS was not increased (9.0 *vs.* 9.2 months) (6). In order to compare radiotherapy to chemotherapy, the GOG-122 study randomized 396 patients with stage III or IV (including patients with maximum of 2 cm of postoperative residual disease) to whole-abdominal radiotherapy or chemotherapy with doxorubicin-cisplatin (7). This study demonstrated, that patients in the chemotherapy arm had a significantly improved 5-year survival rate (55% *vs.* 42%, respectively), although they suffered of greater toxicity. To further improve these results, the GOG-177 study compared the combination of three drugs (doxorubicin, cisplatin and paclitaxel) with filgrastim support (TAP) with standard doxorubicin and cisplatin. This study demonstrated a significantly improved response rate (57% *vs.* 34%, respectively), PFS (8.3 *vs.* 5.3 months, respectively), and OS (15.3 *vs.* 12.3 months, respectively; P=0.037) as compared to standard, but also significantly higher neurotoxicity for the triple drug combination (8). Following this study, GOG-209 compared carboplatin and paclitaxel to the TAP regimen with the aim to develop a less toxic regimen. The findings of this study were that the combination of carboplatin plus paclitaxel was not inferior to TAP in terms of PFS (14 months in both arms) and OS (32 *vs.* 38 months, respectively; HR 1.01) (9). On the other hand, the toxicity profile for the two-drug combination was significantly more favorable as compared to the triple combination, and this regimen became a new standard for chemotherapy trials.

In earlier stages it is very difficult to compare the results of "adjuvant chemotherapy" of the various studies

because of the different eligible criteria adopted. In fact, the characteristics of patients affected with endometrial carcinoma submitted to surgery plus/minus radiotherapy included in "adjuvant chemotherapy" phase 3 trials, range from high risk stage I, through stage IIIC with positive lymph node metastases (10-13). In fact, an Italian study (10) and the JGOG2033 (11) included patients with stage IC with myometrial invasion exceeding half through stage III. In a study of 2 randomized clinical trials (12) one trial (NSGOEC-9501/EORTC-55991) enrolled patients who had cancer in stages I, II, IIIA with positive cytology, and stage IIIC with positive pelvic lymph node metastasis, while the other trial (MaNGO ILIADE-III) enrolled patients who had cancer in stage IIB through III (excluding stage III with positive cytology). In the GOG122 study, patients had stage III cancer with less than 2 cm residual tumor and stage IV cancer (7). The present study (14) encompassed the patient population investigated in previous phase 3 studies of adjuvant therapy rendering the scenario still more confusing. In fact, the eligibility criteria of the Nomura *et al.* study included: high risk stages I, II, III and IV patients who had tumor not extending beyond the abdominal cavity and had 2 cm or greater residual tumor. Moreover, the results of this study are also flawed by the huge percent of the patients who did not complete the planned six cycles of therapy, ranging from 17.1% to 24% in the three arms.

Nomura *et al.* in the conclusions claim that taxane plus platinum regimens did not demonstrate a survival benefit over treatment with doxorubicin plus cisplatin, however, in the subgroup analysis they observed an improved PFS in patients with lymph node metastases treated with docetaxel plus cisplatin or paclitaxel plus carboplatin as compared to those treated with the "standard" doxorubicin plus cisplatin. Thus, at the end of the story the superiority of taxane containing regimens over doxorubicin/cisplatin was not demonstrated, albeit the toxicity, in particular cardiac toxicity, is certainly inferior for taxane regimens which are actually widely used also in adjuvant setting, based on the extrapolation of results achieved in advanced stages studies.

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Footnote

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