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Germ cell tumours

Prof Lorusso: Dear colleagues, we will discuss in the next few minutes, the management of germ cell ovarian tumor. These are my disclosures. So, germ cell tumors represent about 20% of ovarian cancer, but the proportion of malignant ovarian tumors is only 5%. Typically, this tumor affects a younger age group of patients with around 16 and 25 years, typically, in more than 85% of cases, abdominal pain with a palpable pelvic abdominal mass is the onset symptom in most part of patients, but in 10% of patients, also, acute abdominal pain caused by the rupture of the cyst with hemorrhage or torsion may represent the first signal of disease. Tumor marker may help in diagnosis. Typically, alpha-fetoprotein is elevated in endodermal sinus tumor and embryonal carcinoma, and may be elevated in immature teratoma. Beta-hCG may be elevated in pure dysgerminoma, but is always elevated in choriocarcinoma and embryonal carcinoma. Lactate dehydrogenase is elevated in pure dysgerminoma and in embryonal carcinoma and may be elevated in endodermal sinus tumors. LDH and CA125 may be elevated, but remember they are not specific and may be useful during the follow-up. The preoperative workup should be completed with a pelvic ultrasound, abdominal pelvic CT-scan, chest x-ray or CT-scan, and PET-CT that can be added in selected cases. As regarding prognosis. It is well known that the peritoneal staging is a well-recognized prognostic factor. And in our MITO experience, tumors who were not surgically staged, presented a reduced overall survival. Overall survival was 96.8% in appropriately staged patients and 88.7% in incomplete staged tumor. The second most important prognostic factor after surgery is represented by, for sure, stage of disease, but also histotype. And the Yolk sac tumor is a strong predictor of survival. What kind of surgery? Always fertility sparing surgery is what we have to offer to our patients. Also, in advanced disease. Fertility sparing surgery means unilateral Salpingo-oophorectomy with preservation of the contralateral ovary and uterus, and non-fertility sparing surgery should be proposed in post-menopausal women or in patients with advanced stage disease or with bilateral ovarian involvement. And in these cases where the fertility sparing is not feasible, complete debulking should be offered. Remember that systematic ovarian biopsy is not more necessary when the contralateral ovary is macroscopically normal. Is a surgical re-staging indicated in apparent stage 1A ovarian dysgerminoma? This is our MITO experience. 26 dysgerminomas stage 1A patients. 5 of them have received, only 5 of them, less than 20% of patients, have received properly stage in surgery. In this case, we did not offer any kind of adjuvant chemotherapy and none of these patients relapsed. On the contrary, in the incomplete surgical staging group of 21 patients, we offered adjuvant chemotherapy in 7 patients. And no

one of them relapsed. In the group of 14 patients who did not receive adjuvant chemotherapy, we registered three recurrences. So, our conclusion is that surgical staging, completion of surgical staging may be offered instead of adjuvant chemotherapy when there is a place for follow-up. What about adjuvant treatment? In stage 1A dysgerminoma, only surgery is necessary. This patient should not receive any kind of adjuvant treatment; in general, in this kind of tumor, the recurrence rate is relatively low ranging between 15 and 25%. And of most important, patients can be successfully treated at the time of relapse with a high likelihood of cure. So, in this condition more and more space is taking the idea to offer in stage 1 well-staged disease to offer follow-up. And actually, our guidelines report that also in stage 1B and C dysgerminoma, although adjuvant chemotherapy is recommend, there is a place for the active surveillance that can be offered as an option only in patients with properly-staged disease. What about immature teratoma? Again, these are our guidelines. Patients with stage 1A grade-1 immature teratoma do not require any further chemotherapy after complete surgical staging, but also, actually, also, in patients with stage 1A grade-2 and 3 properly stage 2 but with negative postoperative biomarker, active surveillance can be proposed, although it is not accepted by everyone, but we consider it as an option for our patients. Stage 1A grade 2, grade 3, properly staged with a negative post-operative biomarker. And what about stage 1B and 1C tumor? This is our experience with the group of Michael Seckl. We put together our experience in 81 stage 1A, 1C immature teratoma would receive active surveillance and 27 patients who received chemotherapy. And as you can see, although a retrospective experience, it does not seem that chemotherapy impacts on prognosis also in stage 1A, 1B and 1C immature teratoma, properly staged patients with negative postoperative biomarker. But this is a really preliminary experience that possibly will merit further confirmation in a larger series. What about Yolk Sac tumor? Adjuvant chemotherapy is the standard of care in all staged of Yolk Sac tumor, but very recently, a space for active surveillance can be offer in properly staged, stage 1A, 1B tumor with negative postoperative, tumor biomarker. When I speak about active surveillance, I refer to a very strict schedule of surveillance. This is what we have published in ESMO guidelines. In the first year, the physical examination should be done on monthly basis, pelvic ultrasound every two months and tumor marker every two weeks, a chest x-ray every two months and CT-scan every one month. And then, every three months, this is the surveillance during the first year and during the second and third, and fourth year, as you can see, the schedule is really strict; so, it is important in order to offer active surveillance that the patient is being really motivated to follow this active surveillance strategy. What about advanced disease? As I reported also in advanced disease, fertility sparing surgery should be considered whenever there is the possibility to save at least one ovary. Platinum-based regimen is the treatment of choice. And the combination of bleomycin, etoposide and cisplatin is the most used regimen. In terms of number of cycles, it is considered that four-cycles of BEP are useful in patients with advanced disease and three-cycles in patients with completely resected stage 1 tumor. Remember that only, also, when you offer four cycles of BEP, bleomycin should be taken off after the third cycle because of lung toxicity. What about the management of recurrent disease? Likely, these are high-sensitive tumors and more patients are cured after the first treatment; only a few patients relapse, but most relapses are cured within 24 months. Data for salvage therapy are scars and in most part of cases, extrapolated from the experience in testis cancer. The most important prognostic factor seems to be the resistance to platinum, where the definition of resistance is four to six weeks, recurrence of four to six weeks after completion of platinum. And this prognostic factor is very important with long-term survival only 5 to 50% in platinum resistant patients. And more than 50% with the reintroduction of platinum in platinum-sensitive recurrence. What we can offer to cisplatin-resistant patients, the most used regimens are represented by vincristine, actinomycin D, cyclophosphamide or paclitaxel- gemcitabine, or gemcitabine-oxaliplatin. While in platinum-sensitive patients, platinum should be reintroduced in combination with ifosfamide plus or minus paclitaxel, or in combination with ifosfamide and vinblastine or vinblastine and bleomycin. There is a place also for high-dose chemotherapy with stem cell rescue. This may be an option. In this experience, 13 patients recurring with germ cell tumor were treated with the combination of carboplatin-etoposide and support with stem cell infusion. And although, for sure the numbers are not so huge, but 7 out of 13 patients achieved complete response. And for those of 4 of these patients, we have long-term survival up to 27 months and were disease

free. Carboplatin may be an alternative to cisplatin in order to reduce the treatment-related toxicity. And this seems to be supported by this retrospective analysis on 126 patients treated either carboplatin or cisplatin were no difference in term event-free and overall survival were reported. That is a place for secondary surgery? The issue remains controversial, but remember that any resectable residual disease should be removed. This is particularly important in immature teratoma, mainly when we have normal serum biomarker in order to avoid the teratoma growing syndrome. But unfortunately, we have to remember that outside this situation, unlike males, women, whoever relapse with malignant disease after primary chemotherapy have a poor prognosis. So, in conclusion, malignant ovarian cancer germ cell tumor, usually occurring in young women with the most part of cases excellent prognosis. This is the reason why fertility sparing surgery should be considered and offer for all patients to decide to retain fertility, regardless, the stage of disease. Major cytoreductive surgery is usually limited to those patients with residual disease after chemotherapy. Close surveillance actually is an option and is increasingly being offered to patients with properly stage, stage 1 disease with negative postoperative biomarker, if patient accepts to follow the active surveillance schedule. BEP chemotherapy is the most commonly used chemotherapy regimen and patients relapsing after chemotherapy remain a major challenge and they have a lower cure rate with respect to the male counterpart. Thank you so much for your attention.