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e-Session n 617013 - 14th June 2021

Uterine sarcomas

Prof Ray-Coquard: Hello, everybody, it's my great pleasure to be there with you today to share my knowledge on uterine sarcoma and I have to say that uterine sarcoma is a big challenge and you will see not only one big challenge but several we have to manage when we would like to treat these patients. And the first point is that, we have to think not to uterine sarcoma but we have to think to all the different uterine sarcoma. In terms of epidemiology, we have to remember that it is a rare malignant gynecologic tumor, less than 5% of all uterine tumors. The old WHO classification speaks about leiomyosarcoma, low and high-grade ESS and undifferentiated sarcoma and adenosarcoma. You will see that now we have a new classification for this disease. The first challenge, and it is not the last, is clearly to identify malignancy, and why? Because we know that surgery, speaking about sarcoma, is completely different than speaking about a benign tumor. And unfortunately, morcellation in case of malignant tumor will clearly decrease the progression-free survival but also, the overall survival. And unfortunately, all the uterine sarcomas need a large and radical hysterectomy without morcellation. Unfortunately, as you can see on the right-side of the slide, the majority, the vast, vast majority of the tumors are benign. And in this case, is always complex to think to something very rare. In terms of surgery, I would like to remember you some important information, standard surgery includes total hysterectomy. We don't need lymph nodes dissection in the vast majority of the uterine sarcoma. Also, undifferentiated sarcoma can have some lymph node involvement. The vast majority did not have lymph node involvement. Conservative surgery can be discussed but could be debatable for a stage A disease non-menopausal status and clearly, need a dedicated multidisciplinary board before to take such important decision. Unfortunately, as I mentioned before, the majority of the patients were operated as a fibroma with morcellation and it's clearly the big issue. And also, we know that, in this case, re-operation needs to be discussed for suboptimal surgery. I would like to share with you some important information speaking about leiomyosarcoma. We have looked at soft tissue sarcoma, and we have reports that it is not exactly the same overall survival than uterine leiomyosarcoma. It is something important to remember. And we have confirmed these data on progression-free survival also, using the NetSarc databases involving more than 1000 patients. We have a clear difference between soft tissue sarcoma and uterine leiomyosarcoma and probably the quality of the surgery is one of the reasons to explain the difference in terms of overall survival. The second challenge, and I spoke about that before, is to identify the subtype. Effectively, we have a clear difference in terms of prognostic when we speak about stage. Between stage I and stage IV, for example, you see that the five-year specific survivor is completely different. But also, when we speak about histology. And we have now some very important data to consider that adenosarcoma, ESS, are of good prognostic. Leiomyosarcoma is bad. And high-grade ESS, or undifferentiated sarcoma has a very poor prognostic. And so,

it is an important point to consider stratifying management on histology and probably on biology for the future. And the last prognostic factor important to remember is the morcellation impact directly, the progression-free survival and overall survival. The new classification, the new WHO classification has now identified endometrial stromal sarcoma. We have the smooth muscle tumor, including leiomyosarcoma but also, STUMP, leiomyoma, it's a benign tumor. And at the end, we have a third group of miscellaneous mesenchymal tumors including all different sarcoma. In terms of pathology, we have difference in terms of tumoral necrosis, mitotic count and nuclear atypia. With a lot of atypia for leiomyosarcoma, clearly less for STUMP. And, as you can see, we don't have any tumoral necrosis for benign tumor as leiomyoma or mitotically active leiomyoma. But we have some mitotic count in all these different tumors. In terms of biology, we know now that there is several differences between the different subgroups, specifically, for example, for low-grade ESS we have a low mitotic rate but we have frequently ER and PR positive tumor. We have also a fusion gene in this tumor, it's close to 60 to 70% involving just F1. For leiomyosarcoma, if we have some positivity for ER or PR receptor, we have more frequently complex chromosomal abnormality with no specific translocation but a high mitotic rate, a lot of atypia as I mentioned before. And in the high-grade, endometrial stroma sarcoma or in the undifferentiated sarcoma we also have translocation, more specifically involving a YWHAE and also, NUTMB chromosomal gene fusion. And this is clearly linked to some prognostic, we will see later. An interesting thing looking to leiomyosarcoma biology is the P53 mutation that can be reported in close to 60% of the cases. We have also PTEN alterations. We don't have translocation as I mentioned before. We have a lot of chromosomal loss and gain as a clear genomic instability. And it is also mentioned recently, some BRCA2 mutation that can be interesting when we think to treatment for this tumor. One interesting TCGA publication, from three years ago, is to compare the STS leiomyosarcoma and uterine sarcoma. And we have seen, finally, some clear common alterations as P53, Rb1, PTEN. But also, we have identified different clusters in terms of RNA sequencing. We've a cluster clearly hypermethylated when we have seen a cyclin amplification, DNA repair alterations, AKT alterations for the vast majority of this cluster, in general, linked to a worse prognostic. And we have also another cluster more frequently involved in STS leiomyosarcoma, hypomethylated, where we have a lot of NK immune cell involved in the microenvironment and a better prognostic with less AKT-pathway activation. It is interesting to remember for the future. The third challenge is to consider what happens after optimal surgery. Is there any benefit for radiotherapy? This slide reports the big randomized trial already published in the literature by the EORTC. Unfortunately, as you can see on the slide, we don't see any benefits specifically for leiomyosarcoma but also for ESS to receive radiotherapy versus observation, not for progression-free survival. Also, no benefit for overall survival, only carcinosarcoma. But we know now that carcinosarcoma are not sarcoma, have some benefit to receive radiotherapy. The other challenge is about adjuvant systemic treatment for leiomyosarcoma but also, we can discuss for high-risk sarcoma, high-grade ESS, adenosarcoma overgrowth or undifferentiated uterine sarcoma. What about low-grade ESS? And what about systemic treatment? We speak about hormonal therapy, chemotherapy or targeted treatment. In terms of LMS, we had several phase II trials in the past and randomized trial who seem not to report any benefit to add adjuvant chemotherapy, including doxorubicin versus observation. Including combination of chemotherapy with adriamycin, platin, and ifosfamide versus radiotherapy alone. All these two randomized trials did not report benefits for PFS or overall survival. We have also retrospective data who compare patients receiving adjuvant chemo versus radiotherapy versus observation. And all of these retrospective data, finally, did not report benefit specifically for uterine LMS stage I, comparing any systemic treatment versus nothing. However, we have two phase II in the literature reported by the GOG, including gemcitabine and docetaxel, where results seem very good compared to previous data using only old-school chemotherapy or only doxorubicin. These two-phase II reported in the literature push us to move to a big phase III, exploring the combination of gemcitabine, doxorubicin, docetaxel compare to observation for leiomyosarcoma stage I in adjuvant setting. Unfortunately, these trials need to include more than 200 patients, only include 38 patients. And the primary point is overall survival. The result reported by Martin Hensley, two years ago, unfortunately, did not report any benefit for these patients, no benefits for progression-free survival. Also, we have very few patients but

also no benefit for overall survival and more specifically, less overall survival in the adjuvant setting compared to observation. So, today, we can see there that effectively randomization of chemotherapy versus observation is a challenge in rare cancer. We have a lot of issue to include patients and adjuvant chemotherapy does not provide an overall survival benefit in patient with leiomyosarcoma stage I disease. And so, we have to consider observation as a standard of care until now. In terms of high-grade ESS and undifferentiated sarcoma we don't have any randomized trial, just retrospective or prospective observational studies. And it seems that perhaps, patients receiving chemotherapy have perhaps more benefit compared to observation. It is only a trend but it is also very few patients not significant, but looking to the worst prognostic of this disease this can be discussed for patients specifically where the patients are young and very proactive to receive adjuvant treatment. In terms of low grade, we don't have to think to chemotherapy, only hormonal treatment. The question is, what about any benefit to add adjuvant hormonal therapy for early-stage disease? It is frequently used, but again, we don't have any randomized trial. We have some retrospective data in the literature where it seems that patients receiving adjuvant hormonal treatment seems to have less relapse than patients who did not receive adjuvant hormonal therapy, specifically, in advanced stage III and IV. But in terms of overall survival, we don't have any data to consider adjuvant hormonal therapy because we don't see any benefit until now. So, the role of adjuvant hormonal treatment is to be discussed. And we need to wait to systematically, to think to adjuvant hormonal treatment for early-stage. For a patient with metastatic disease after complete resection of the metastasis, we don't have, again, any data to support a strong rationale, but can be discussed. And it will be nice to have randomized trials in the future. The fifth challenge is to consider the need for a front-line therapy in advanced disease. It is the current GCIG ESGO guidelines for these patients. We discuss systematically for local recurrence, vaginal or pelvic or isolated recurrence to think to local treatment, surgery plus or less radiotherapy. And we discuss systemic treatment for disseminate disease. What it is for also algorithm coming from the sarcoma world, it is exactly the same. We think to isolated lung metastasis to have surgical treatment in addition to systemic treatment. We retrospectively look at the survival of the patient with a soft tissue sarcoma and we have reported that surgery of lung metastasis can increase overall survival compared to patients who receive only chemotherapy. And so, for patients needing systemic treatment we have several data from the literature to help us to decide. First at all, we don't have seen any benefit using mono-chemotherapy versus combination. There is a big randomized phase III from the EORTC including not only uterine sarcoma but all soft tissue sarcoma, including uterine sarcoma. We don't see benefits in terms of overall survival. We have seen some benefit in terms of response rate and median PFS. So, combination can be discussed if we consider that response is an important point for the patients, specifically for symptomatic disease but we have to remember that combination increases the toxicity of the treatment. In terms of treatment, we always hoped that gemcitabine plus docetaxel could be an interesting combination compared to doxorubicin. Unfortunately, the recent paper from EORTC, including, again, not only uterine sarcoma, but also, soft tissue sarcoma, this trial did not report benefit in terms of PFS or overall survival to use the combination compared to doxorubicin alone. And so, doxorubicin remains the gold standard in palliative situation. We also have another failure adding olaratumab to doxorubicin. We have several interesting results in the randomized phase II trial in terms of median PFS but also, in terms of overall survival and response rate. And looking to that, we observe benefits in the uterine sarcoma specifically, leiomyosarcoma. Unfortunately, the phase III trial was not positive and this combination, finally, did not report to be superior to doxorubicin alone. Another failure is adding bevacizumab to gemcitabine and docetaxel. This randomized trial was published by the GOG and unfortunately, we don't see any benefit in terms of response rate, median PFS and overall survival adding bev. to this combination in uterine sarcoma. Why so many failures? It is a question of drug using doxorubicin for all sarcoma. It is a question of heterogeneity of tumor and prognostic. We don't know exactly, but we have seen some interesting data retrospectively for example the EORTC database has reported how leiomyosarcoma soft tissue or uterine sarcoma are more sociable to the combination of doxorubicin-dacarbazine than doxorubicin alone or doxorubicin plus ifosfamide. We also, have looked at these questions specifically for uterine sarcoma. And we have seen effectively that ifosfamide alone did not

report a great response rate in this population of patients compared to the combination of cyvadic or doxorubicin alone. It is an important point. We've also seen that gemcitabine plus dacarbazine increase overall survival and PFS over dacarbazine alone. It is an important publication from the Spanish group and this is really helpful in routine practice. There is also what I have mentioned before, this TCGA analysis who explains how this tumor could be completely different at the molecular level. And I mentioned this publication in terms of BRCA mutation specifically in the uterine leiomyosarcoma, 10% of these patients have BRCA mutation. And so, I hope that the future of the biology can be really helpful to consider completely different drugs, perhaps a platin or PARP inhibitor for patients with genomic instability and BRCA mutation. At the opposite, amplification of cyclin needs to be treated by other drugs, probably, doxorubicin can be good. So, we need to learn more about the heterogeneity of these patients. And finally, we have a recent publication for Carlson, who have reported how the molecular classification can be completely different in the same localization including undifferentiated uterine sarcoma. We have some clearly linked to immune profile where interferon can be an interesting biology to use in this population. We have also angiogenesis and aggressivity for some clusters of patients. We have some where hormonal receptor can be interesting, et cetera, et cetera. So, we need to clearly develop more translational research for uterine sarcoma before to decide about the treatment in the near future. The next question is what about the treatment after doxorubicin? We have a combination of trabectedin plus doxorubicin reported in the literature. This is a phase II coming from the French sarcoma group reporting huge results in terms of response rate and median PFS in this phase II trial. And we are clearly waiting for the LMS04 trial exploring the doxorubicin alone versus a combination in first-line to see what happened in terms of combination and perhaps we'd be able to change our practice in the near future. We have also anti-angiogenic agent reported in the literature, the pazopanid, regorafenib, and also anlotinib who reported interesting data in sarcoma patients. And for this reason, we are also waiting for the results of the cabozantinib trial dedicated to uterine sarcoma, high-grade uterine sarcoma, including undifferentiated sarcoma, including high-grade ESS, including leiomyosarcoma. These patients, after a first-line of chemotherapy, including doxorubicin alone plus or less ifosfamide can be randomized for non-progressive disease to receive cabozantinib for two years versus placebo. And this trial will close in June, and will be, I hope, available next year. The last challenge is what about specific treatment according to histology? I mentioned before how trabectedin can be interesting to use in leiomyosarcoma. We had several publications in the past, not including only uterine sarcoma but it seems better than carbazine alone. We know that in uterine LMS trabectedin seems to be better than all the other drugs explore in the past. It is a GOG presentation. And so, all these data are clearly in favor to using trabectedin for leiomyosarcoma. We don't know about high-grade uterine sarcoma, but this could be the discussion later. We also have to remember that trabectedin needs to be continue until progression and not stopped. It is again, a randomized phase II trial from the French sarcoma group who reported how it is important in terms of PFS to continue the treatment and not to stay after six cycles. I already mentioned the combination of dacarbazine and gemcitabine for leiomyosarcoma. It's interesting to mention this combination. And we also have to think to hormonal treatment for uterine LMS, where ER and PR expression is reported. We have retrospective data reporting positive effect of hormonal therapy, more frequently aromatase inhibitor in this population of patients. That can be a good opportunity for patients with indolent tumor. In terms of immune therapy, unfortunately, until now, we don't see so much activity using PD1 or PD-L1 inhibitor in leiomyosarcoma. And I have to say that perhaps we will see better results. We had a small number of patients until now and probably immune therapy alone by PD1 will not be the future for all uterine sarcoma. In terms of other publications, we have several data to be consider. I mentioned pembrolizumab just now. We have also publication of mTOR inhibitor in uterine leiomyosarcoma with some interesting response rate. Also, we don't have any randomized trial. The combination of olaparib plus trabectedin could be interesting for leiomyosarcoma specifically, those with genomic instability. As mentioned before, we are waiting for the LMS04, we've quite exciting data from the phase II. The PembroSarc will be perhaps interesting and cabozantinib as mentioned before. And so, if I would like to give you a summary by subtype. For endometrial stromal sarcoma of low-grade, you have to remember that the prognostic and the treatment is clearly linked

to histology. And so, you need to review the pathology to be sure about the quality of the histology and the grade. You have to remember that until now, we don't have any data to consider adjuvant treatment for a localized completely resected tumor. In case of low-grade, you need to think only to hormonal treatment and consider chemo after all the different links of hormonal treatment that can be used before to move to chemotherapy. In terms of undifferentiated sarcoma, it is a very aggressive disease. The majority of these patients have an advanced stage. So, we need to consider chemotherapy plus or less radiotherapy for these patients. We don't have any prospective data. So, we recommend to include these patients in a clinical trial. In terms of active agent, we know that doxorubicin is probably one of the best. Combination can be discussed looking to the symptomatic disease. We know now, we have some translocation but unfortunately, at the moment, we don't know how to target this translocation. And we need clearly international collaboration for this tumor. In terms of leiomyosarcoma, you have to consider surgical management only. Total hysterectomy is the recommended surgery, no morcellation. You have to remember that the risk of metastatic disease is more than 50%. So, it is an aggressive disease. Radiotherapy did not improve survival until now. We don't have any benefit reported in the literature with adjuvant chemotherapy. In first-line chemotherapy, doxorubicin alone can be discussed with olaparib for BRCA mutated patients. If we can, it could be interesting to know that. Activity report for ifosfamide is very low. So, I don't think that ifosfamide could be the best. Trabectedin is a good option. Also, gemcitabine plus or less dacarbazine. Pazopanib can be discussed also. And as mentioned before, parpi for a BRCA mutated leio. could be interesting. In terms of future, what could be the future for these patients? It could be forced automatically randomized trial. We can discuss before to develop randomized trial a way to consider all uterine sarcoma and looking to the histology to decide about some drug. We can also consider several drugs looking to some biology abnormality and at the end develop the randomized trial as we would like to see in the near future. You have to remember that these patients need to move and to be referred to expert centers for the management but also for a central pathological review. The proper diagnostic work-up will be the best to be sure about the quality of the surgery and to avoid intralesional surgery. Systemic treatment and surgery in metastatic setting can improve overall survival. And we need to continue to explore new drugs and new strategies because currently the overall survival of these patients is very poor. Thank you very much for your attention.