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Particle therapy in the treatment of gynaecological cancers

Dr Barcellini: Good evening. It's a pleasure to be here with you this evening. And thank you, Dr Lorusso to be here with me. I'm Amelia Barcellini, and I'm a Radiation Oncologist. at the National Center for Oncological Hadrontherapy. And in this presentation, I will talk about the role of particle therapy in the treatment of gynecological tumors. My disclosures, and this is my agenda. In the first part of my presentation, I will talk about the clinical meaning of hadrontherapy and the radiobiological and physical characteristics of the particle. In the second part, I will talk about the role of hadrontherapy in gynecological cancer. And at the end, I will summarize the current evidence about particles for gynecological tumors. So, what is hadrontherapy? Hadrontherapy, as known as particle therapy, is an innovative and promising form of radiation therapy using heavy particles, such as protons and carbon ions that compares to photon beam radiotherapy and has dosimetrical and radiobiological characteristics. From a dosimetrical point of view, particles have advantages of that dose curve. I mean that while x-rays decrease their energy exponentially with the dose, the green line. Particles and, in particular, protons, the red line, and the carbons, the blue line, are able to deposit most of their initial energy at the end of the range that is within the Bragg peak that is within the tumor. From a radiobiological point of view, particles have a higher LET that ensures a higher relative biological effectiveness compared to proton beam radiotherapy. And because of the higher LET and a higher RBE, particles are able to induce more serious damage to tumor. For example, oxidative stress and a double-strand breaks to DNA. The double-strand breaks to DNA are the most lethal damage that can lead to a massive loss of genetic information and cell death. In particular, carbons are independent on fractionation, on cell-cycle stage, and are active also in the most radioresistant phase of a cell cycle. And above all, are independent on the oxygenation in the tumor. That's for the physical and radio-biological characteristics, particles are able to spare normal tissue and to increase the dose to the tumor. And are more effective to hypoxic and radio-resistant cancer. So, are suitable for tumors that are closer to radiation sensitive organs, for example, bowel spinal cord and brain, slow growing tumors, hypoxic tumors, or, in case of recurrence, after a photon beam radiotherapy. In gynecological oncology, particles have proved to be safe and effective for the most radio resistant histologies such as adenocarcinoma of the cervix, or gynaecological melanomas but are also suitable for inoperable endometrial carcinoma in particular, in patients unfit for brachytherapy and in case of recurrence in pelvis after photon beam radiotherapy. The current evidence. Locally advanced cervical cancer. In 1994, at NIRS, clinical trials of the user of carbon-ion radiotherapy for locally advanced cervical cancer started. And the first trials are two phase I and two dose escalation trials that showed, first, that the local control was promising in particular for very advanced disease, maybe for the hypoxic component in the tumor, then, that the maximum tolerance dose to the rectum was a 60-Gray Equivalent. And then, finally, that a whole pelvic irradiation with carbon is safe, and that despite the good local control, the systemic control was poor, maybe, for the absence of combination with chemotherapy. The protocol 9902 is a on 22 women with locally advanced cervical cancer from stage IIB to stage IVA, IVA, for a

bladder invasion in which 8 patients had already positive nodal status. The tumor size was mainly more than 5 centimeters. And these women underwent a total dose to the cervical tumor that ranged between 64 to 72-Gray Equivalent over 20-fraction. And after a median overall treatment-time over 36 days and a median follow-up for surviving patients of 116 months, the five-year overall survival, it is the green line, was 50% and the five-year local control, the blue line, was 68.2% with mild toxicity. And interesting is that higher the dose the better the local control, with a cutoff for the dose of 70-Gray Equivalent. Even if the local control was promising, the disease-free survival was scant because of the relapse in para-aortic and the scarce systemic control. In order to improve the para-aortic control, the protocol 0508 tested the safety over an extended-field carbon ion radiotherapy on 26 women with a median age 59-years and locally advanced cervical cancer from stage 2B to stage 4A, 20 women had already positive nodes and the tumor size was mainly more than 5 centimeters. This protocol followed a shrinking field approach with a total dose to pelvis and para-aortic nodes up to 39-Gray Equivalent over 13-fraction. An additional 50-Gray to GPV and surrounding tissues. And a final local boost up to 18-Gray over 2-fraction. The total dose to the cervical tumor was 72-Gray Equivalent over 20-fraction. And indeed, the local control as well as the overall survival, improved if compared with the previous study, but 26.9% of the women experienced a distant failure. The para-aortic control was better than the previous study with only one case of failure in para-aortic and a rate that overall was 5.3%. And the better control was for smaller GPV with two years and five years local control that ranged between 86% for a small tumor, to 67% for a larger tumor. Interesting is this phase I and II clinical trial about the more aggressive and radio-resistant histologies that is the adenocarcinoma of the cervix. It's a clinical trial on 55 women with locally advanced cervical cancer and a tumor size that is mainly more than 5 centimeters. These women underwent a total dose to the pelvis that ranged between 62.4-Gray to 74.4-Gray over 20-fraction. And the local control is promising. And also, the overall survival, if compared with the historical data on a photon beam radiotherapy with or without chemotherapy. But, in order to improve the progression free survival and the overall survival in adenocarcinoma in the protocol 1001 concurrent chemotherapy was tested, it's a study by Okonogi, in 2018, and these women with locally advanced adenocarcinoma were treated up to a total dose of 74.4-Gray Equivalent in 20-fraction with a concomitant weekly cisplatinum administration. And the overall survival at 2 years was 84%, the blue line, with a local control at 2 years of 74% and improved, compared to the previous studies. These data are also confirmed by the score matched analysis in 2020, by Okonogi, that compared 26 women who underwent carbon-ion radiotherapy upfront, versus 26 women who underwent a combo-approach with weekly cisplatinum and carbon-ion radiotherapy for adenocarcinoma. The median age was 57-years and the median follow-up period was 34 months. Interesting, is that the local control was not influenced by the combination with chemotherapy but the overall survival and the distant metastatic free survival was significantly better in the combo arm compared to the carbon-ion radiotherapy alone, with a toxicity that is a similar between the two groups. Another histology, melanomas. Gynecological melanomas are really rare and radio-chemo resistant tumor with a 5-year overall survival that ranges between 50% for vulvar to 10% for cervical melanoma. Actually, there isn't consensus or guidelines about the management and the treatment of this rare disease, but treatment as well as the management, are based on the current data concerning gynecological cancer and cutaneous melanoma. Surgery, when feasible, is the gold-standard especially for the early-stages. But sometimes, it's a challenge because of the close proximity of bladder, anus, and rectum. Adjuvant treatment is unproven. And it's also unproven radiotherapy in the adjuvant setting even if it's reported that in some patients with the positive surgical margins or histologically positive nodes. The largest series about the use of carbon-ion radiotherapy upfront and radical dose for gynecological melanoma is a retrospective analysis of 37 patients by Murata, in 2019. These women had a unresectable malignant melanoma and were followed for a follow-up period that is over 23 months overall and 53 months for the survival. Mainly, these women had vaginal and vulvar tumors and only in 3 cases patients experienced a cervical tumor. Nine women were treated for recurrence after surgery. And three women underwent chemotherapy before carbon-ion radiotherapy. And the most used fractionation scheme was 57.6-Gray Equivalent over 16-fraction. About the outcome within six months, 19 women experienced a complete response, 14 women a partial response, and 4 a stable disease. 30 women

achieved a tumor disappearance following carbon ion radiotherapy and 15 patients had died before the final follow-up, but four died from non-cancer related reasons. And the local control at two years, the red line was 71% and the overall survival at two years was 53% with a milder toxicity. Interesting is that none of the factors analyzed, so, age, previous treatment, stage, tumor size, nodal status or the tumor response within the six months after carbon-ion radiotherapy influenced the local control, the progression free survival and the overall survival. But the age was associated with the rate of distant metastases. In fact, the younger group with an age less than 71-years experienced a higher incidence of distant metastases compared to the elderly group. Inoperable endometrial cancer. The largest series about the treatment upfront for endometrial cancer is a series by Irie, in 2018. And it's a pooled analysis of data from two trials about 14 women with a stage from first to 3C of endometrial carcinoma that are considered inoperable because of the co-morbidities, age, or refusal of surgery. These women underwent a total dose to the tumor that ranged between 62 to 74.4-Gray Equivalent and at six months after carbon-ion radiotherapy, 10 women experienced a complete response. And the complete response was influenced by the total dose with a cutoff of 70-Gray Equivalent. No patient experienced higher acute or late toxicity. And the five-year local control was similar to the surgical data without an adjuvant treatment. Okay. And finally, the challenge for a radiation oncologist, the re-irradiation for pelvic recurrence. Pelvic recurrences are still a challenge for radiation oncologists due to the proximity of bowel and the total dose received by bowel, rectum and bladder in the previous treatment. And the largest series about the use in a curative setting of carbon-ion radiotherapy for pelvic recurrence is a retrospective series of 16 cases described by Shiba, in 2017. These women had unresectable recurrence at the edge of the previously irradiated field and at a median age of 57-years and a median tumor size of 27 millimeters. These women underwent carbon-ion radiotherapy up to a total dose that ranged between 48 to 57.6-Gray Equivalent according to the previous dose to the bowel. The toxicity was milder in earlier and later settings. And the local control was impressive with a 3-year local control, the blue line, of 94%, a 3-year overall survival, the red line, of 74% and a disease-free survival at 3 years of 55%. Indeed, 2 women experienced a local recurrence and 7 women had distant metastases. My conclusion. Hadrontherapy appears to be a safe, effective, and feasible treatment-approach that show advantages over photon beam radiotherapy. In particular, for locally advanced cervical cancer, carbon-ion radiotherapy provides promising local control in women receiving pelvic carbon-ion radiotherapy and para-aortic carbon-ion radiotherapy with concurrent chemotherapy. And carbon-ion seems to improve outcome in the adenocarcinoma of cervical cancer compared to photon beam radiotherapy, maybe, for the advantages in terms of radio-biological characteristics of particles. But prospective and randomized clinical trials are warranted in order to confirm these data. For inoperable, endometrial carcinoma and gynecological melanoma, carbon-ion radiotherapy upfront at a curative dose, shows similar therapeutical effectiveness to that of surgery. And for the radio-biological and physical characteristic, re-irradiation with carbon ion radiotherapy could meet the expectation as a curative treatment option. But I think that a strong collaboration between researchers and physicians treating these rare and radio-resistant tumors and difficult to cure tumors is of utmost importance to make a step forward in the treatment of this disease. And thank you for your attention.

Dr Lorusso: Thank you, Amelia. Thank you for this very comprehensive and interesting review on the role of particle therapy in the treatment of gynecological cancer. I take the opportunity to remember to our colleagues to ask you questions because we will take advantage of your presence here. You are one of the most important experts in Italy about this technic and this strategy. The first question arrived through the Q&A chat. In your experience, Amelia, how could you manage a relapse which is very close to the bowel? Do you consider this a contraindication to particle therapy or what kind of instrument do you use to reduce the bowel perforation?

Dr Barcellini: Well, thank you for the question. Yes. Bowel is a challenge for re-irradiation because it's a very radio-sensitive organ and sometimes, is a dose-limiting factor, but as happened in other kinds of radiation treatment, the position of a spacer between tumor and bowel has proven to be safe and effective in re-irradiation patients. And in our experience often we ask to our surgeons to create space between the

recurrence and the bowel by the installation of a spacer made by [Audio Not Clear] or a muscle flap or also a silicone and create a space, lead to transform a palliative treatment into curative treatment because bowel is safe.

Dr Lorusso: There is another question for you. Are there some studies that your institution is carrying on with this technique?

Dr Barcellini: Yes. In our institution, there are several trials ongoing and for several tumors, and for gynecological tumors there are two clinical trials that are to phase II and prospective clinical trials about the use of a carbon-ion radiotherapy upfront for gynecological melanoma, at first diagnosis on recurrence after surgery and unresectable. And the name of this protocol is Cycle. The primary endpoint of this trial is the progression free survival at 2 years and the secondary end points are overall survival and local control, as well as quality of life. And the idea is to reproduce in a prospective setting the retrospective data of Japanese experience. The other trial ongoing in our center about gynecological tumors is CYCLOPS. It's a phase II prospective study about the use of carbon-ion radiotherapy upfront for recurrence in pelvis after a photon beam radiotherapy. These recurrences are unresectable and often strongly closer to the bowels, so, difficult to cure, difficult to treat. And the first endpoint of this trial is the local control at 2 years and the secondary endpoints are overall survival, progression free survival and quality of life. And there are several centers, several oncological hubs in Italy that are involved in these trials.

Dr Lorusso: Amelia, are you informed of any trial directly comparing radiation treatment with carbon particles therapy in any setting or in any disease?

Dr Barcellini: Yes, there is a clinical trial with carbon-ions versus photon beam radiotherapy for locally advanced pancreatic cancer and it's a randomized clinical trial with several institutions.

Dr Lorusso: This is another really interesting question for you. In the trials you mentioned that are ongoing in your institution now, are there involved different professionals? How do you consider important multidisciplinarity in this field?

Dr Barcellini: Okay. Yes. I think it's crucial. As happened in other fields of medicine, also, in hadrontherapy, the multidisciplinary is of utmost importance. And I think that it must involve several highly skilled professionals from several fields of medicine from surgery to gynecology, to oncology, medical and radiation oncology, pathology, biology, and so on, but from a quality-of-life perspective, I think that it could be worthwhile the role of a psychologist and a sexologist also, considering that often these are women are reporting a negative impact on a sexual functioning that leads to a negative quality of life and a negative wellbeing.

Dr Lorusso: In this regard, Amelia, I'm very curious because you reported the dosimetric advantage of carbon particle therapy with respect to radiation treatment, traditional radiation treatment, but in front of this, the toxicity was completely more manageable with other therapies. In my mind, in front of an increased activity sometimes, in most part of cases, we reduce the increased toxicity because as you clearly explained most of the dose reaches the tumor. How can we explain this different toxicity profile of the two techniques?

Dr Barcellini: Between photon beam and carbon ions?

Dr Lorusso: Exactly.

Dr Barcellini: Okay. It's related to the ballistic characteristic of the particles and especially the characteristics of carbons that are able to release their energy at the end of their range, that is the Bragg peak. And the dose after the Bragg peak falls down. And the so, the dose to the entry channel, but also in the exit channel, falls off very quickly. And in this way, the organs at risk are spared.

Dr Lorusso: Very, very, very interesting. In one of the trials you showed, the local control was very high but in order to increase distant control the combination with chemotherapy was performed. The trial was carried in a Japanese population. Are you informed about similar trials in Caucasian population because you know that there is a general consent that the Japanese population have differences in terms of genotyping, with respect to Caucasian population and this explains the different efficacy, but also different toxicity in the treatment? Are you informed about similar trials in Caucasian patients?

Dr Barcellini: No. The only trial about carbon-ion radiotherapy for gynecological tumors now open is the CNAO trial for melanoma and recurrence and there isn't a trial about locally advanced cervical cancer. So, no.

Dr Lorusso: But your trials are in combination with chemo or proton therapy alone?

Dr Barcellini: Only carbon-ion for recurrence and a sandwich approach if it's indicated. And for melanoma, a sandwich approach with immunotherapy, when indicated, but not in concomitant.

Dr Lorusso: Really interesting. I want to underline the really amazing results you reported for melanoma. All the gynecologists connected here well know how is difficult to treat recurrent vulvar and vaginal melanoma and the data you show are really, really interesting. While in the meantime, our colleagues ask other questions, what is your view looking at the future? What is your view of this strategy in gynecological malignancies? Where do you find a place for this technique, methodology of treatment in all the three gynecological malignancies? Because you did not mention ovarian cancer; you know that ovarian cancer has been considered a disease not to treat with radiation treatment because it is a widespread disease, but very rapidly a lot of data are coming about radiation treatment in some particular histotypes. So, for instance, for the Clear cell tumor, but also, for a BRACA mutant, high-grade serous in the terms of stereotactic radiotherapy. Do you find a place also for particle therapy in specific setting of ovarian cancer?

Dr Barcellini: Okay, well, it's a good question. Yes. I think that an important approach could be a combination with PARP inhibitors and immunotherapy with particle therapy in different settings. In fact, we know that PARP inhibitors can improve the radio sensitivity in the tumor. And we know that immune therapy with carbon-ions, but also with radiotherapy can improve not only the local control but also, the progression-free survival inducing also the well-known abscopal effect. So, considering that in-vivo and in-vitro studies carbon ions are proved to be more immunogenic than photon beam radiotherapy and can induce abscopal effect, a prospective, maybe, for our patients could be the combo immuno and carbon-ions also to create evidence and create data about the safety and the effectiveness. And in particular, it could be worthwhile for locally advanced cervical cancer or recurrence after cervical cancer, immune therapy, or considering also the new classification, the molecular classification of endometrial cancer also for high-risk endometrial cancer. So, P53 mutated, maybe. And in other settings, yes, the ovarian cancer with a PARP inhibitor and considering also that there is a lack of data about the user of high-dose radiotherapy also with photons and a PARP inhibitor. So, a study in order to compare SBRT maybe or IMRT for photons, versus carbon ions and protons with PARP inhibitors can be worthwhile to create evidence to test safety and to evaluate also the efficacy. And in other settings, I think it could be a comparison between SBRT and carbon ions or proton beam radiotherapy in women with locally advanced cervical cancer that are unfit for brachytherapy because considering the impressive data from Embrace 1, Embrace 2, Retro EMBRACE analysis, brachytherapy is not an option, and that is mandatory but in a clinical practice, we know that a lot of women are unfit for a brachytherapy for several reasons, for example, an extension of the tumor or a refusal by the women or also the anatomical situation. So, I think that find a better alternative, a good alternative for these patients is a high-priority in radiation oncology.

Dr Lorusso: Very interesting. So, we have also another problem, which is unavailability of brachytherapy, you know that in Italy, but probably across the world, not all the radiotherapy departments, have also brachytherapy facilities. So, this could be a good setting in which create an alternative for our patients. For

sure. I want to ask you a very provocative question. In Italy, we have only your site performing particle therapy until now, and probably, this reality has not spread across the world; why in your opinion? Is there a problem of sustainability also, with respect to radiation treatment? What is the thought of particle treatment?

Dr Barcellini: Okay. Yes. Sustainability. Sustainability is an important issue in radiotherapy and in hadrontherapy. In hadrontherapy, in particular, because there are a small number of the centers that are able to deliver particles and that are able to deliver both particles, carbons and protons. Worldwide, there are only six hubs that are able to deliver carbons and protons, three in Europe. And I think that the reasons are different. The first is the need of a larger place to create this hub, compared to the hub to install the photon beam radiotherapy. Then that Hadrontherapy is more expensive than photon beam radiotherapy, of course, and also, that it needs a highly skilled professional, with a long learning curve. You know, another reason could be that the tumor treatable with carbon-ions has a small incidence. So, a small number of centers, small incidents of tumor can lead to a call for an international collaboration in order to centralize these women, these patients and in order to create evidence and in order to make also the rarest more treatable, I think. And from a cost-effective point of view, in my opinion the way to create evidence could be also use a scientific method such as the comparison between treatment plan with competitive radiation treatment, such as SBRT, IMRT, versus IMPT, or carbon-ion radiotherapy. Or use NTCP model that is a model that evaluates the normal tissue complication probability. And I think that a combination of these approaches could be informative and also effective and feasible in particular, to find the better treatment approach and tailored approach for our patients.

Dr Lorusso: Thank you so much. The last short question, with a short answer. You well explained you work in a multidisciplinary setting and I expected that you discussed all the cases that were referred to you for treatment. What is in your opinion and in your experience, the main clinical contraindication to this treatment which preclude patients who receive it?

Dr Barcellini: Okay. In my experience, the exclusion criteria for recurrence, for example, is the infiltration of the bowel and the impossibility to create space between bowel and the tumor, because the treatment wouldn't be safe if the bowel is infiltrated or in a strong proximity. And also, I think that also the invasion of veins or vessels could be a contraindication without a prothesis in these vessels.

Dr Lorusso: Thank you so much. I want to sincerely thank you, Amelia, for this great presentation. The last burning question from a colleague. What are the long-term effects of proton therapy and how does these incidents compare with conventional radiation treatment?

Dr Barcellini: Sorry, can you repeat that?

Dr Lorusso: The long-term effects. If they are more or less compared to conventional radiotherapy.

Dr Barcellini: Okay. Is less the late toxicity compared to photon beam radiotherapy because of the radio biological and ballistic characteristic, that I've already explained.

Dr Lorusso: Thank you again for this interesting and comprehensive presentation. You impassioned all of us to the use of particle therapy in gynecological cancer. Thank you so much. And thank you to all the attendees for staying with us.

Dr Barcellini: Thank you. Bye.