Subtitles and transcriptions
Subtitles and transcriptions are available for selected materials for purpose of helping users understand the contents of the educational sessions.
Uncertain words have been indicated with ?? before and after the part. Parts that could not be understood at all have been indicated as [Audio Not Clear].

Every effort has been made to faithfully reproduce the audio of the sessions as recorded. However, no responsibility is accepted for mistakes or omissions. ESO does not endorse any opinions expressed in the presentations.

e-Session n 574 - 27th May 2021

Frontiers in bone marrow transplantation for acute leukemia: Total Marrow/Lymphoid Irradiation

Prof Bruno: Good evening everyone. Thank you for joining this very interesting meeting organized by Dr Filippi. And it's my honors to give you a few words of introduction before Dr Vagge's presentation. Bone marrow transplantation is a curative treatment for many hematological conditions, nowadays, both for non-malignant and malignant and particularly, in adults it's very important for the treatment of acute leukemia both myeloid and lymphoid. Total body irradiation has always played a role in bone marrow transplant. There's always had an historical role and actually, decades ago when the first transplants were experimented, myeloablative total body irradiation was indispensable to transplant our patients. Unfortunately, TBI, myeloablative TBI is associated with a very high toxicity and only a few patients, those young patients who were medically fit could undergo a transplant. There has been a great evolution over the decades and now myeloablative total body irradiation is primarily used in acute lymphoblastic leukemia or in some aggressive lymphomas where the diseases are very aggressive and really need an intensive, potent myeloablative conditioning that could eradicate the disease. But a breakthrough in the application of irradiation in bone marrow transplant happened in the late nineties, early 2000 from the Seattle group where the no-myeloablative TBI was applied in the conditioning regimens of our patients. And that was very important because it was primarily immunosuppressive rather than myelosuppressive, but in clinical practice, at that point, we could transplant also elderly patients because all the reduction of the toxicity of a conditioning regimen. But there were other evolutions along the way, total lymphoid irradiation in most recent years. And lately, total marrow irradiation has always had a role and probably, will play a role in elderly patients. So, in those frail patients where not toxic conditioning regimens can be applied. So, in a nutshell, we can tell that total body irradiation in different forms has always been very important for decades and the evolution has allowed to widen the possibility its application. Historical role, but also, a present role that will be discussed with Dr Vagge. Over to you, Dr Vagge, and thank you for being here with us.

Dr Vagge: Thank you, Professor Bruno, and thank you, Andrea, for the kind invitation. I'm honored to be part of this group. I know very well your great experience in this kind of setting of patients and in part, hematology and oncology settings. I like to take the presentation or the introduction of Professor Bruno with my first slide because radiotherapy or a radiation oncologist never won a real Nobel prize but in the case of bone marrow transplantation with Donnall Thomas, the role of TBI was really, really important in the winning of this prize, like for Madame Curie. So, radiation oncology during the years, in the science, is always following important settings and important treatments in the setting, sorry. In the setting of the bone marrow transplantation or hematopoietic stem cell transplantation, the beginning of the role of radiotherapy is really linked with the role of the transplantation as well and starting from ablative role with TBI for lymphomas or

solid metastasis, the evolving role of this technique changed during the evolution of this kind of transplantation, both in autologous and in allogenic ones. During the last 10 years, a new development like total marrow irradiation, tried to change the role of radiotherapy in this setting of patients. We know very well what are the strict role of radiotherapy in this kind of patients. So, radiotherapy, it's important to have no barriers in the anti-leukemic effect and make more spaces in the bone marrow. And also works with a great immunosuppressive effect. And this is in only one therapy, you can reach all these kinds of options and without a great toxicity at all, but we know very well that the first inferences in the setting or in the outcomes of the allogenic transplantation is linked from the donor type. And also, from the kind of transplantation that we are moving to. During the last year, most of the centers tried to implement haploidentical transplantation to reach a faster donor and a faster transplantation to treat faster the patients without delay, during the waiting for the sibling matching donor. We know very well that different regimens of conditioning are linked to the effect that we are looking for and these kinds of conditioning are specifically linked to the donor and to the higher-risk of the disease. And TBI in this setting was tailored also by dose and fractionation to achieve these kinds of results. But it's not easy in the scenario of the multiple settings or multiple regimens of allotransplantation to define exactly how is the importance or always exactly the role or the effect of the total body irradiation by the comparison of so different, so great differences between regimens of chemotherapy regimens. We, nowadays, or in 2010, we know that TBI was the standard of care in some settings of patients acute ALL and in respect of UC but intravenous busulfan was better in some groups of patients with AML. Nowadays, these results are confirmed by more recent reviews or retrospective analyses of these kinds of patients but there is still a subgroup of patients that is the subgroup of patients with very high-risk of disease. That, probably, need something more than the conventional treatment of the conventional strategy didn't obtain yet. If we compare some results from the retrospective analysis of Andrea Bacigalupo in 2010 with the paper published in 1977, 30 years of differences of from the two groups, the outcomes of these acute advanced leukemia patients didn't change so much, but we know very well or at that time, in 2007, we know that TBI in chronic graft versus host disease were directly linked to a reduction risk in death. And we know also very well that increasing the dose of a radiotherapy with higher doses of TBI with a different kind of fractionation, we can reduce the relapse of disease in this group of patients, but at the same time, we know very well that increasing the dose of radiotherapy will reduce also the probability of long-term survival because the high toxicity after a dose range that we cannot overcome with a conventional technique due to many acute and bub-acute and collateral effects. It's not so easy to overcome these limitations with TBI. In some kinds of words, we can try to modify with a conventional technique these limits by modifying the biology or the fractionation like usually we can do in some solid tumours, but this is not an easy way to achieve a goal, these kinds of goals. Some groups also demonstrate that BID-fractionation of TBI the conventional 2 Gray per day versus 4 Gray single-fraction per day, it does not seem to have differences in acute toxicity, but at the same time, this will not help us to increase the dose to the tumour or the dose to the whole body. Some groups try to develop more advanced techniques of total body irradiation, more easy to take it reproducible in a modern radiotherapy department and very advanced techniques. But nowadays, all these techniques do not allow us to an increase of radiation dose. So, since 2009 and in 2011 the first report comment on transplantation and the role of total marrow and total lymphoid irradiation should be better than conventional TBI. After 10 years, a recent review, very nice review reported that this kind of technique probably is moving forward to be a new standard of care in a specific group of patients, potentially. We know very well that with this technique, that it's a really advanced technique, we can spare most of the body or most of the healthy organs in the body from 40 to 60% of the dose that we prescribed to the bone marrow and with the Thermo bone marrow we talk about all the bone or the skeletal bone of the patients and this technique it's quite complex in the setup, in the planning or also in the delivery. So, we push a little bit the conventional radiation technique and we designed around the world with some groups the specific setup setting that would be helpful to make reproducible and so advanced technique. It takes some time from the planning, from the setup and also, to the delivery of the patients with a daily dose of 4 Gray per fraction, potentially, we need to fulfill a slot of more than one hour and a half and two hours. This

technique should also be performed with conventional Linac, but conventional Linac needs a bit of more complexity, because this kind of Linac needs more field junction. And this could give the potential of increasing the range of error that we can achieve with this technique. But the delivery dose is complimentary and equal probably with the one that we conventionally do with helical tomotherapy. This high-precision of technique allows the clinical, the clinician or the radiation oncologist also to re-treat patients that have been already treated also for ablative regimen, like in this case after a multiple myeloma patient already treated, previously treated over a vertebra. But during last years, several groups collaborated together to reach what is the best way to deliver this kind of treatments and also, to do it faster as possible. So, these groups are encouraging all the groups around the world to collaborate as much as possible to open a niche in a technique like total marrow irradiation. With this introduction of the role of TMI and the technical aspects of TMI, the question is if we can go forward and a new reduced toxicity conditioning in allogenic transplantation. What we well-know that we have to myeloablate and post-immunosuppress but also, we need to remember that we have also to rescue from the myelosuppression. So, we need to limit also the toxicity to stem cell, the bone marrow stem cells. We know very well that a hematopoietic stem cells are more radio sensitive. But there are some cells that are mesenchymal stem cells in the bone marrow that are more radio-resistant and the mesenchymal stem cells potentially are the reason or the ones that help also for the re-engraftment after transplantation. And we don't know exactly always the limit of those, that these subgroup of stem cells can reach. And we don't need to arrive to the limit of the no engraftment. So, if we take a look for a conventional treatment with total body radiation, the blue lines, we know that all the body is reach a conventional dose of 12 Gray but with an increasing dose with the conventional sparing of the organs with the TMI, we can hypothesize that 20 Gray is a feasible dose over all the bone marrow with a reduction dose tolerability and tolerable to all the organs of the body, like in a conventional total body of 12 Gray. There are some clinical records during the last 10 years that should help us understand always the potential of total marrow irradiation. Most of these studies obviously are a phase I or pilot studies. The numbers of patients are quite low but are still increasing during the last years. What I think that should be interesting to report and to analyze are the data from the group of the City of Hope that was first in the world pioneering this kind of technique, and this group, one of the last reports from this group it's about the increasing of the dose up to 20 Gray, like the question that we had few slides ago. So, most of these patients were very advanced patients, or in second relapse, also with active disease. And what we can find after this dose escalation is that the outcomes in terms of progression-free survival, and overall survival were quite interesting or really, really with a high interest in terms of leukemia control. So, the effect of radiation or radiotherapy is really high in this setting of patients and probably, this would be a goal to follow in the evolution of this kind of technique. One of the questions that arise in the first part of the development of this technique was the risk of extramedullary erupts that could be achieved if you do not treat the whole body. And if you concentrate the irradiation dose only on bone marrow, but after the first 100 and more patients treated at City of Hope, the responses and the retrospective analyses showed that there was no increase of extramedullary relapse with total marrow irradiation in respect with the conventional treatments. Another setting of really interest in transplantation setting of patients, it's the old patients. And from these data, from the European bone marrow transplantation registry, we can see that the tendency is to continue to transplant or to increase to transplant also patients with higher age and in this setting of patients potentially with a reduced intensity conditioning regimen, the role of selective radiotherapy could be really helpful. Some reports recently showed that a few toxicity in RIC patients with acute leukemia or advanced leukemia with a median age of 55 but patients were treated up to 70-years-old and this kind of treatment with the total marrow and total lymphoid irradiation both together showed that only the relevant delayed toxicity reported was 35% of radiation pneumonitis or probably less than 35%. And this is a really, really important result to follow in the prospective of new clinical trials to define. Also, recently have been published also the ultimate project that is Haplo for elderly with high-risk leukemia. It's a study from the group of Perugia. Perugia it's quite famous around the world because they perform Haplo transplantation with the cell the depleted and with also the increasing... With the purification of CD34 and Treg and Tcon and it's a quite complex transplantation setting

but the high profile of results in anti-leukemia effect it was increased by the use of a selective radiation dose or technique like total marrow radiation. Recently, also, have been revise the role of radiotherapy in the setting of the transplantation in multiple myeloma. Multiple myeloma is conventionally treated with autologous transplantation and sometimes with autologous and tandem autologous or autologous and allogeneic transplantation. And there is likely a better outcome during the last five years. We can see in this light, but it is still a high-risk disease. And it's really difficult to cure. A Polish group recently analyzed the role of the potential of total marrow radiation in 12 Gray, in a hypofractionation regime with 4 Gray per fraction every day, and a boost of FDG PET positive region before the transplantation. If we have a FDG positive patient before transplantation, potentially, these kinds of patients are really high-risk patients. But if we look at the results of these preliminary reports, we can see that the overall survivals per year are really high and also, there is a very good progression-free survival a five-year with a toxicity profile of a grade 4 and grade 3 really low, also, especially, in the first autologous transplantation. The one that was performed with a total marrow irradiation in the setting of the chemo preparation. This technique, this so advanced and complex technique could be also potential. Could also give potential advantages also in the treatment of the setting of pediatric patients that, as already Professor Bruno presented in the introduction, are a different setting of patients but the role of TBI has been recently validated and probably it's more strong the role of TBI in acute lymphocytic leukemia in pediatric patients than in adult ones. But we know very well that one of the reasons why this study was performed, was because, in many cases, the pediatric patients need to avoid the toxicity of radiotherapy. In some kinds of cases, we know that the late effects of radiation therapy due to inhomogeneity of radiation dose or potentially higher doses to some organs particularly radio sensitive could be a heavy cost after 10 or 20 years. Like it can happen in this kind of subgroup of patients. So, the potential role of a selective radiotherapy with a homogenous dose and potentially defined or designed over also the sanctuary areas that are so important also in a child, could be helpful and could be really a potential opportunity in this setting. To conclude with a few slides this presentation about the new role of total marrow irradiation in the setting of transplantation, one of the things that are so important during...also, in evolution during the last years, are the radiomics, are the concept of radiomics or the new imaging functional and potentially predictive of response. In the setting of TMI, what we know very well is that within the bone marrow there are different areas, some hypoxic areas, but are also some areas with mesenchymal stem cells or with mesenchymal cells or with the leukemia stem cells. But it's really difficult to figure out where exactly this subgroup of areas are. Usually, we perform single biopsy or a double biopsy, but we know exactly what happens in a specific point. It will be really important to have a picture of all the body or all the bone marrow in the same moment to have an idea of how all bone marrow changes before and during and after the transplantation and also, the radiotherapy treatment. With this technique, we know exactly all the doses we delivered in each part of the bone marrow. And this could be helpful to selective biopsies or also, with a whole-body analysis, with specific traces like FLT-PET or dual-energy CT, that conventionally are nowadays used in every radiotherapy department also for the simulation of the patient. So, we have many information under our eyes that we can try to develop and use to identify which parts of the bone marrow are modifying, especially, we can follow the modification of the red into yellow marrow, potentially, yellow marrow with adipose sites, it could be a sanctuary for leukemic stem cells. And this could be helpful to identify subgroups of areas that could be the new targets of a higher dose than 20 Gray, that we know that nowadays we can reach. But if we can boost with the subregion, at high-risk of disease, potentially, we can and improve much more that we actually can do with this new technique. These are to conclude the... It's difficult to read, but my message was not to show you in the specific parts what are the ongoing protocols, but how many are they ongoing protocols worldwide? And this could be interesting, and it seems it means that the TMI it's really a reality that it's developing and with a good potential in terms of control on acute and high-risk disease. To conclude and to thank you all, I suggest you to read, if you are interested in this argument, that it's a book about total marrow radiation with many experiences of many centers from around the world. I would like to thank you all for the invitation and I hope to have been clear enough. Thank you.

Prof Filippi: Okay. Great. Thank you so much, Dr Vagge, for this comprehensive overview of what are the biological basis, technical basis, and clinical application of total marrow irradiation worldwide. I would like to open the discussion with Professor Bruno just trying to summarize a few points. For adult leukemia, I see a space for total marrow in two fields. First one is trying to reduce morbidity of TBI, but in adult patients, I have to say that probably the morbidity is not too much related to growth impairment or a secondary tumour, et cetera, it's much related to acute toxicity or for example need a long-term complication of the combination of radiation and the chemotherapy. So, it is a primary endpoint to reduce toxicity but in adult patients, some colleagues, I think, that may argue that probably TMI is too expensive, is too time consuming, is too selective, just for reduce toxicity. So, this is my first point. Otherwise, for high-risk patients, I see a very important role of TMI in increasing the dose to the bone marrow with a similar dose profile to organs at risk. So, probably, in my view, we should implement trials with total marrow radiation, also, including centers not using tomotherapy, because we need to think about expanding the indications to the centers worldwide. So, we cannot limit the use of TMI to a few centers in the world, using very high technology because this will never be applied by any transplantation unit. So, my first point is, what we would like to do in adults, to reduce toxicity or to increase results? And in my opinion probably the idea of escalating the dose to 20 Gray, up to 20 Gray in the bone marrow, could be a reasonable one. For pediatric patients, is probably the opposite. We have very good results with 12 Gray of TBI, but we have a very high-toxicity, especially, for children treated below 3 years of age or below, in any case, pre-puberal children. But I also have to say that in children TMI is very difficult to perform and we need to have a complete collaboration with the anesthesiologist, we probably need to sedate all patients, all children, because the treatment is taking about one hour. And so, I would like to discuss with Professor Bruno these points in light also of the new therapies for leukemia. Do you see a role for TMI in escalating the dose for adult patients with leukemia in special situations? Do you see a role for reducing toxicity? And even if you're not a pediatric oncologist, what is your vision for the future of this therapy in children?

Prof Bruno: Thank you, Andrea. Well, I think first of all, speaking of the adult setting. I think not only can we reduce toxicity with TMI but also increase the therapy overall, because if you consider that you irradiate the marrow, residual disease could be treated also with TMI and we can increase the dose for transplant, for example, but also for in general, in elderly patients and frail patients also to be a good consolidation for previous chemotherapy. We know that in acute leukemia, in elderly patients, we don't have any particular curative strategies, there are new agents that are very promising, but they usually prolong the survival but do not have any curative intent. So, if we consider those patients, with a new agent, enter complete remission, at that point exploiting TMI, we could also think of a transplant at a very old age, but it's not considered really eligible for transplant right now. So, I think that the elderly fit patients who suffered from leukemia in the late Sixties, early Seventies could be really a fraction, a subset of patients but where we could really try to design trials to define the role of TMI. And at that point, if the toxicity is not high using the lower doses, I think we can increase, as you said, to intensify the marrow irradiation, and you could even get more results in terms of clinical outcomes without really increasing the toxicity. So, that's the way I see TMI in an adult setting. As we said, there are many differences in the pediatric setting. And I think the technical difficulties probably are the most difficult to overcome and actually would defer back the answer to my pediatric oncologist, honestly. But I think that there will be a role, especially, in those patients who can reach a CR and you can think of a consolidation of a previous therapy or conditioning regimens for transplantation.

Prof Filippi: Okay, thank very much, Benedetto, for your answer. Dr Vagge, do you think that's... Also taking into consideration what Professor Bruno said, do we have the possibility, the space and the support from institutions for thinking about randomized trials in TMI? Do you think we should only rely on phase II mono-institutional, such as for example, the experience of City of Hope? Is it enough for employing TMI in adults as the Professor Bruno said? I mean to be sure that the toxicity is okay and then, go ahead with a step further, or we need randomized phase III trials? Because in this setting, it's very difficult to think about a randomized phase III trial. What is your opinion about that?

Dr Vagge: My opinion is that it's really difficult also from the hematology point of view performing randomized phase III trials in the setting of allogeneic transplantation. I think it's not easy and also, it's not easy without the support of high industry, you know very well, how much is the cost of a big trial, randomized trial, phase III trial. And this is a question that usually comes in the field of radiotherapy with the new techniques. We had this question also for IMRT, at the beginning of IMRT. I'm not sure that we need a randomized phase III trial. Potentially we can move on with randomized trials but phase II trials. And after that, focus on a new technique. And then, if you have a new strategy, you can compare this new strategy with the results from phase II randomized trials, because we are sure that this technique is better than the other one, the old one; it's better in terms of the efficacy or in the potential, but we don't know, what we'll lose on the road, with this new technique.

Prof Filippi: Professor Bruno, do you think... Are you confident as an hematologist in performing TMI? For example, if you had the opportunity, moral, to talk with your radiation oncologist and just say, okay, let's close the TBI program and open a TMI program. Are you confident with the data we have on the 12 Gray dose with TMI, or do you think that you and your colleagues will be a little more skeptical in using total marrow because they don't have long-term survival data of randomized phase III trials?

Prof Bruno: Okay, that's a very good question. I think I wouldn't be... I would welcome a a program with TMI, honestly and we already talked about that with our radiation oncologists. And there are data from City of Hope that are very encouraging. And I think the experience could be different at single centers, experience may differ from one another, but I would be very enthusiastic to start a program in TMI. And especially, as I said before, in frail patients, elderly patients, where you do not really have many curative options and maybe, with gaining experience, we could also increase the dose, but I think with the current dose that we heard about and with the data coming out from City of Hope, I would be very enthusiastic to start with those data, with that application.

Prof Filippi: Okay, great. So, I think that's the hematology world it's quite enthusiastic. We obviously need to think about the methods and the settings, et cetera, but you think that probably elderly and fragile patients are one of the settings. This is interesting because, sometimes, this is a different setting from the dose escalation, one, Stefano, but there are two different patients' subgroups. For the first one, you use TMI for optimizing radiation delivery in a setting of patients at high-risk of toxicity. And in the other setting, you are trying to perform TMI to enhance activity in high-risk patients. So, in an ideal world, we should start with the trial involving the two subgroups of patients. Just briefly, I would like to... I have a question from the audience, what is the experience with the role of TMI, MLI in a relapsed/refractory acute leukemia so, patients at the highest risk of recurrence and it is only an option in the relapsed setting or is it something that we can perform with confidence? What do you think?

Dr Vagge: In the first setting, in the frontline setting, potentially, we continue to use TBI and ALL due to the lower need in increasing of the dose. And we need...I think that you pointed out all the correct aspects of the problem with this kind of technique. It is still quite time consuming, but also, it needs a larger effort in the department, not so, big, but a quite large effort. And you need to focus all the attention over those kinds of fields. If you reach an important result in high-risk patients, potential, you pull all the research following this kind of new technique, but on the other way, if you concentrate your attention on high-risk patients, it's a much more difficult also to put in evidence or underline what are the potential benefits in a group of patients with a very high-risk of disease. And they also are not so easy to show nice outcomes. Like professor Bruno told to us before, the last result presented by the City of Hope group with patients with acute myeloid leukemia, with active disease, treated after 20 Gray, with a good response on active disease. This is an important result that we have to follow because on the other way, a conventional technique is still good enough in the treatment in the frontline acute leukemia patients, adults, obviously.

Prof Filippi: Yeah, I see that. So, probably, technical problems are gonna be... I hope that they're gonna be resolved by technology, by an improvement also of a very fast in artificial intelligence driven planning that in my opinion with probably overcome the technical problems in about four or five years, but not now. And so, I think that, as Benedetto said, probably, if you want to start a program now you need to think about starting with TMI in adult patients, fragile, elderly, et cetera, being quite sure that probably you will have the same results with lower toxicity. It is very logical. It's also a pragmatic approach. On the other side, probably, if you want to open a new window of opportunity for patients with a relapsed/refractory high-risk leukemia, you need to start in any case another trial because in my opinion, for example, my colleagues from the transplantation units do not feel that the City of Hope data are sufficient for delivering 20 Gray to the bone marrow. I don't know exactly how we can answer to that because it's very hard to perform a trial comparing 20 - 12, in refractory high-risk relapse disease, 20 versus 12. It's very unlikely. But don't know, Professor Bruno, what do think about that?

Prof Bruno: Yeah. To summarize from a hematological standpoint, I think it's difficult to establish the role in very refractory patients, where there are no other treatments. So, in the ideal scenario, in my opinion, it would be better to start trying to reproduce the data already available and try to find a subset of patients where theoretically TMI can really play a role. And I was thinking, actually, not to be kind of boring, but in those elderly patients who cannot undergo a conventional transplant, but are in CR, I think TMI and the transplant, because of age and medical conditions, could be really a good way to start, especially to acquire experience in centers who are naive to the technique. In terms of refractory patients, I think that refractory patients are so difficult to treat nowadays and with new agents, even with a total body irradiation. So, I think it would be really difficult to setup a program using the TMI in that subset of patients. I will start really where theoretically we really think that there's a role for TMI.

Prof Filippi: Okay, thank you very much, Professor Bruno and Dr Vagge. Unfortunately, I would love to continue to discuss with you, but we have to close this session that has been very interesting in my opinion. And I hope that all the colleagues who will attend to this session offline over the next days and weeks will find it useful for opening at least a debate or an internal debate in the transplant groups about the the implementation of new techniques of radiation therapy in bone marrow transplantation. So, thank you so much, Stefano Vagge, from the University of Genova, San Martino Hospital, in Genova, and Benedetto Bruno, from New York University and it has been a pleasure to have you both today in discussing this topic and have a nice morning or afternoon or evening and thanks also to European School of Oncology for hosting us. And I'm gonna close the session. Once again, thank you and bye-bye.