European Perspective on Myeloma Treatment Strategies with Dr. Antonio Palumbo

One of the worlds best Myeloma doctors, Dr. Antonio Palumbo will be be with us on this show.

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Dr. Palumbo will be explaining his myeloma treatment approach Fit/Unfit/ Frail classification and use of auto transplants.

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Unlike the US, in Europe, recruitment for Myeloma clinical trials is much higher and the treatment drugs are also different.

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Join us to learn how Myeloma treatment is different in Europe.

Full Transcript:

Priya Menon : Hello everyone and welcome to Curetalk for the discussion on multiple myeloma. I am Priya Menon, Scientific Media Editor at Cure Talk, joining you from India and I wish everyone here a very happy new year. This is Cure Talk's 76th episode and we have a new website now. Please do visit us at www.curetalk.com and do send in your feedbacks to me priya@trialx.com We are discussing European perspective on Myeloma Treatment strategies and we have with us on our myeloma broadcast today one of the foremost myeloma specialist in the world. Dr. Antonio Palumbo from University of Torino. Welcome to the show Dr. Palumbo. It is an honor to have you here.

Dr. Antonio Palumbo : Thank you very much for the invitation

Priya Menon : My cohost for the show is Myeloma survivor and editor of myelomasurvival.com Gary Petersen. On the panel are Myeloma advocate and survivors Pat Killingsworth, Jack Aiello, and Lizzy Smith. Gary Petersen will introduce us to our expert and begin the discussion. Before I hand over to Gary, I would like to tell all listeners that we will be addressing questions send in towards the end of the show and if you have a question for our panel you can press 1 on your keypads and we will bring you on air to ask your questions. Alternately, you can email me with your questions at priya@trialx.com. With that its over to Gary. Gary you are on air

Gary Petersen : Thank you again Priya and thank you for putting together this wonderful forum for all the patients to be able to learn some of the best new news and the existing procedures in multiple myeloma. Dr. Antonio Palumbo is the chief of the myeloma unit of the Department of oncology division of Hematology, at the University of Torino. Dr. Palumbo was research associate at the Wistar Institute university of

Pennsylvania. He specializes in hematology malignancies, medical oncology and as clinical and research interest in plasma cell dysplasia, whatever that is. I did not google that. Dr. Palumbo is MD, received his doctorate degree from the University of Torino in Italy, Served his residency in internal medicine and fellowship in Hematology, Oncology at the University of Torino He is a member of the board of directors of the international myeloma society of the advisory broad of international myeloma foundation, the IMF. President of the European Myeloma Network trial group. He also is a leading leading several multidisciplinary projects on molecular biology, pathogenics of multiple myeloma in the development of biological markers to predict clinical outcomes. He is also well published over a hundred publications in peer-reviewed journals as well as numerous abstracts in several text book chapters. And in recognition of all his significant accomplishments, Dr. Palumbo was recently given the award by the international myeloma foundation, myeloma research in patient care international myeloma foundation honored him with the Robert, 2014 Robert A Kyle lifetime achievement award So, Obviously that is, and I had to cut a lot of stuff out too Antonio, I got to tell you. This should be one busy guy, so thank you so much for taking the time to visit with us.

Dr. Antonio Palumbo : Thank You for the Invitation

Gary Petersen : Ok. So Welcome to the CurePanel and With the spending per patient in the USA twice that of the EU and the EU having the average reported survival rate as good or better than the US, I would say “Europe Does More With Less”. So, Today we will be discussing the European perspective on Multiple Myeloma with you Doctor and learn more about the European Myeloma Model. Now at ASH and ASCO it appears there is a cooperative relationship between researchers throughout the world with a large degree of commonality. Yet there also seems to be differing views on treatment protocols. Would you outline what these differences in treatment are, and why there are differences? For example Dr. Hari mentioned the US and EU have similar patient populations but the EU performs 7 times as many Allo transplants for myeloma. In addition, in the US does only uses the auto transplant for treatment and in only 18.6% of patients. I would have thought myself that it was greater than that and I was wondering if Europe does more than that and If transplant (early or late) is a backbone therapy, you know why isn’t it significantly more than may be in the 60 to 80% range? Would you

Dr. Antonio Palumbo : Congratulations

Gary Petersen : talk on the subject doctor?

Dr. Antonio Palumbo : Yes, Well I would say first that the collaboration between EU and US is very important and I think all the achievement that has been made until now has been due by an international expert specially for this type of rare disease an international collaboration is essential and I think we learn from both the sides of the Atlantic, that something we learn from the other From a clinical perspective i would say that first message is that myeloma is a rare disease and a specially for patients the first message is you should ask how many myeloma patients the given doctor is to see every single year. Because this is making the major difference. Of course a center where they can see more than 100 patients per year, do have a completely different experience and approach from a center, might say, see only 5 patients per year. So the first important general message for patients is go in centers where a given center or physician receive at least 100 patient per year. Otherwise the risk is that you are seeing a wonderful physician, but once again the professional attitude is coming from exercise an exercise which a number of event cannot be so few and unfortunately unfortunately fortunately myeloma is a rare disease, so its not so easy to have a wide experience. This I would say is the first issue. The second issue is probably related to the fact that to some extent, the world is going towards a more specialty approach and before we were mixing all the oncology, mixing together hematology and solid tumors With time they are trying to separate oncology from hematology and even in a very specialist center we are moving to even disease specialist a myeloma specialist, lymphoma specialist, a leukemia specialist and so on. So, generally speaking of course going to a disease specialist might be better, but I don’t think this is essential. What is essential is being a center where the experience is of at least 100 patients per year. Having said that, which is the last question was on transplantation, I would say that an allogenic transplantation is concerned, this is not really standard for

multiple myeloma. Today the indication for allogenic transplant is first of all within clinical trials, so cannot be considered a standard of care. Second it might be used in very young subject, younger than 55 or 60 in early relapse, first, second relapse after diagnosis. Not, the use of allogenic transplant is not suggested today at diagnosis. Of course outside clinical trials. As autologous transplantation is concerned, these have been a huge discussion between the international community. Europe has been always more in favor of autologous transplantation, US to some extent has been more reluctant to the use of autologous transplantation, up from the at diagnosis. Today we already have two randomized studies, clearly showing the benefit of autologous transplantation at relapse, instead of keeping that These procedures, later on, sorry, autologous transplantation at diagnosis instead of keeping this approach for relapse So today, I think there is clear indication for the use of autologous transplantation at diagnosis. One of the major finding of this study was that only 50% of patients who collected stem cells at diagnosis, they really received autologous transplantation at relapse, for several reasons co-morbidities, different indications, but the first information is autologous transplantation at relapse can be delivered in the bad possible condition only in 50% of patients And therefore, we certainly loose the opportunity of autologous transplant, if we delayed these procedure after diagnosis. The last issue would be that these studies, big show both improvement in remission duration and overall survival. So, they with the available information the evidence is that autologous transplantation must be delivered at diagnosis.

Gary Petersen : So what is your percentage at the EU. Ours is 18.6

Dr. Antonio Palumbo : No we are 50%. We are 50% because, let's say we had to start in UK actually. This is an incident that is basically come form UK. So we do not had the really numbers coming in from all over Europe, the issue is that in Europe we might say that there are 50% who receive autologous transplantation at diagnosis. You might consider that 15-20% of plan, they do not receive it for comorbidities, because of cost you need to be in good clinical condition to receive a transplantation. In other words if you want generally speaking 15-20% of patients do not receive it for a geographical condition because of course, to receive an autologous transplantation you need to be in the big centers. If you live in a small town far away from big cities, it may be not so easy to find a transplantation unit and the last 15-20% is probably related to physician attitude, might not suggest or consider this opportunity for those patients at diagnosis.

Gary Petersen : All right. We have the FDA in this country. Seems to us that our drug approval process goes at a snails pace. In the EU you have the European medicines agency or the EMA, and, is it more effective, do you think than what we have here in the US.

Dr. Antonio Palumbo : Not as much. Don't worry. It is much worse, this is minus here.You see probably form a general point if view, the plus of Europe is that the treatment is more homogeneous, there is more public institutions, everybody is receiving the same treatment so there is more homogenous treatment approach. The minus is that certain is much more bureaucratic, so for example drugs such a Carfilzomib that you do have in US, is not yet available in Europe. And on top of that, probably also you know some economic constraint in Europe is also reducing the opportunity to receive a given drugs for mainly for economical reason. Of course the situation in Europe is different than US because in Europe, generally speaking the drug free for all citizens. So what for you is a cry but insurance in the fore is based on the contract that between the subject and the insurance, here the contract is between a nation and reimbursement. So one nation may decide to reimburse the drug another might not consider the drug cost effective and will not reimburse the drug. So here it is more state based insurance approach.

Gary Petersen : So the, even though the EMA may approve it may not be approved by the nation.

Dr. Antonio Palumbo : Well no, the process is, let's say EMA is equal to FDA. The both evaluate that the drug is effective and not toxic period. Then every single nation as a give insurance from your side, might decide if they do reimburse that drug, they do not reimburse the drug, they limited the delegation for that given drug. So then the nation, as per you the private insurance will decide when and how to reimburse the given treatment.

Gary Petersen : When I view Europe, I see that you are one of the thought leaders in, as matter of fact in myeloma, and as a matter of fact I think, you, and I hope you take this as a compliment, is the Bart Barlogie of Europe.

Dr. Antonio Palumbo : Not really. But, I mean, he did really a lot in US, has changed completely the way it has been.

Gary Petersen : Also Pat Killingsworth just had a blog-post article on his blog, that says, arguably, you are the best myeloma specialist in Europe. But, in the US, I see a disparity between the best institutions, and you mentioned it about the 100 patient requirement that you see as a necessity, that the best institutions have newly diagnosed life expectancies of 8 to 10 years or more vs. the average for both the US and EU which is about 4 years. Do you see the same experience in Europe that the best institutions provide life expectancy 2-3 times that of the local oncologist.

Jack Aiello : This is Jack. One thing I would do is try to clarify with respect to transplant percentages are you talking about all transplant eligible patients that is either 18% or 50% or is that of all myeloma patients.

Dr. Antonio Palumbo : Yeah, all the transplant eligible patients.

Jack Aiello : Thank You

Gary Petersen : Ok. What percentage of the total population would that be Dr. Palumbo?

Dr. Antonio Palumbo : The total patient would be 30%.

Gary Petersen : Yeah, Ok. Our transplant…

Dr. Antonio Palumbo : With your point of view it would be 30%

Jack Aiello : So, its closer than you think?

Gary Petersen : Yeah, it is. Thanks Jack. It definitely is (inaudible)

Dr. Antonio Palumbo : On the total patient would be actually 15 so

Gary Petersen : Ok, the it is very similar. Alright, What I would like to do now is, you had already mentioned that the best institutions, you pretty much answered my 3rd question, that the best institutions generally have significantly better life expectancy than those of the average, and I was just asking whether that was the same in Europe, So let's go on to the questions now. Jack your questions?

Jack Aiello : Yeah, I have couple of them. Dr. Palumbo I am always appreciative of your focus on quality of life and that was evident again at this past ASH when you presented result of the efficacy of getting Carfilzomib once a week instead of twice a week and I think that might be very important trial for patients considering the big difference of, you know, going into an infusion center once a week instead of two consecutive days that is required now. Along those lines could you say more about the categories of fit, unfit and frail patients, what that means and what that might mean in terms of treatment recommendations

Dr. Antonio Palumbo : Yeah,Well, thank you very much for the question. I would say generally speaking the first issue is, Yes, Carfilzomib is probably moving from a twice weekly infusion to a weekly infusion and probably, of course, we have to finish trail B but, this might represent equivalent efficacy with of course more friendly approach and improvement in terms of quality of life, of course avoiding go to the hospital twice a week From the fit, unfit and frail, I think that is very important issue that should become really a standard in every single center, which is the definition. Over the age of 65 we start to question and of co-morbidities might increase dramatically with age. So the issue in few words is first, age by itself and the cutoff is around

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80 years of age. So someone in perfect clinical condition and 81 years becomes unfit person. The second is the presence of co-morbidities and I would include within the co-morbidities of course, lung abnormality, heart abnormality, renal abnormality or liver abnormality that are not due by myeloma but are existing. So subject with these abnormalities do have a higher risk of adverse events during treatment and should be treated with a low dose intense approach in order to reduce the risk of toxicity. The third issue is what I call the lack of each of us. With time our mobility might be reduced, so for me to walk, to go to an hospital, to drive might start to represent the patient. And this is something to take in consideration when we decide which is the most appropriate therapy, because of course, oral administration at home or a twice weekly infusion might also take in consideration which are my mobility capability. Third is also important is my how is my mindset. Some is not well known, but 50% of subject over the age of 70 are unable to take properly the treatment has been administered at all, because they forget it, because they don't recall which pills has been taken or not, and this is another important piece to put in the evaluation, because of course, how I am able to follow my prescription, to do exactly whet they should do is very important to have an effective treatment. So I would say there are these four major evaluation to perform and one is age – very simple, presence of major co-morbidities, mindset and mobility.

Jack Aiello : Thank You. Can you answer, its my impression that clinical trial recruitment to clinical trials is seemingly more difficult in the US than it is in countries like Italy and France. Why is that if I am correct?

Dr. Antonio Palumbo : This has been always a big question for me always too, but basically the answer is mix of different approaches. Say, Here the health care system is mainly public and to some extent there is more trust in the health care system, because the public employee might interest in deliver A vs. B is very limited, you know, my salary is absolutely unchanged by the type of treatment what I am doing. So these these to end (inaudible) from one side, form the other side, being a public official is giving to a higher rank that what we suggest is the right thing to do. I think this is to some extent one of the reason The other is different attitude in the population between the EU and the US. EU more used to do by your self, you have to define what is the best thing to do. We delegate much more to some one else. The public our big Papa, is going to take care of us suggesting which is the school suggesting which is the healthcare, giving us the pensions, so we tend more to delegate to other our major choices Probably in the future we get very close to the US, today I think we are seeing a shift towards US attitude but today this might still be considered a difference.

Jack Aiello : Thank you and the last is a very quick question, Why does it, not that we like steroids at all, but why does it seem like the steroid of choice in Europe is Prednisone rather than Dexamethasone or Dex as is it is in the US?

Dr. Antonio Palumbo : Now can you repeat it. No we use Prednisone instead of dexamethasone.

Jack Aiello : Yeah

Dr. Antonio Palumbo : Well, actually this is mainly for historical reason. We are coming from Melphalan, Prednisone stories, so there is you know a use of Prednisone which is more pronounced in US. I have to say that once again Dex should be considered choice number one for a younger, while Prednisone is certainly a more gentle approach and certainly gives major advantage in, once again elderly frail population. 40 mg of Dexamethasone is not a piece of cake. Pressure might increase, diabetes, you know sleep problems might come, so you know is pretty intense deliver. So to some extent Prednisone I would say is a more gentle approach

Jack Aiello : Thanks so much for all you do for patients Dr. Palumbo. That's it for me Gary.

Gary Petersen : Ok. Thanks Jack. What I will do is I have Lizzy Smith next online Lizzy, your Questions?

Lizzy Smith : Hi, So, I am still very fascinated by the world of Allo transplant for myeloma. Because it seems to be curative I am just wondering your thoughts on why it is not more commonly used an approach to

fighting this disease.

Dr. Antonio Palumbo : Because allogenic transplantation, you know with time, we are, you know, years ago, we were having a sort of chemo that was basically really toxic agent and nothing else. We are starting to have that more, we call it intelligent or smart drug that are really affecting the mechanism of grow of the tumor. So this is the change that we have been seeing, and we will probably see even more in the future, looking at the therapy of 20 years ago and the therapy of today which is the limitation of allogenic transplant. Basically allogenic transplant is an immunotherapy because you are infusing in a given subject Lymphocyte and antibodies where you do not know anything. At the end of the day, the issue is you might create an immunotherapy access myeloma and bingo! This is certainly a success. But you can also infuse and deliver immunotherapy again first, and then when you see the graft vs. host disease, when you see a risk of that, that is still, then certain % within the first 100 days. So the issue is for allogenic transplant, we do not know what we do re-infuse, if you create a major graft vs. host or a graft vs myeloma. The balance of these two options is basically making no difference in comparison to autologous transplantation. Randomized studies comparing autologous transplantation vs allogenic transplant, do seem some such advantage for allo, in other studies advantage for auto. When you put all together there is a major advantage of one procedure vs the other, so evidence today, that is why we do not suggesting, from a clean pure clinical point of view, is that on general population, you cannot say that Allo is better or Auto or vice versa. On a single subject I call it Russian Roulette, we might infuse major graft vs. myeloma bone marrow and this is a plus, or a major graft vs. host and this is a minus, unfortunately we are totally unable to predict these two options.

Lizzy Smith : Ok, thank you.

Dr. Antonio Palumbo : Thank You.

Gary Petersen : Ok Pat your questions?

Pat Killingsworth : I am back. Sorry about the glitch Gary.

Gary Petersen : Yeah, I am sorry doctor that we did have a glitch.

Pat Killingsworth : Pressed the wrong button on a phone I don’t use very often Hello doctor

Dr. Antonio Palumbo : Hi

Pat Killingsworth : I too has questions about using Allogeinc transplantation in Europe, but I think you answered that very well. It would be nice if we knew how it would turn out, wouldn’t it? Because I have a number of friends including Jack on this broadcast who lived a long time after undergoing an Allogenic transplant, so it is always helpful for those of us that are late stage patients thinking if we could have done something like that maybe we would be around a little longer.

Dr. Antonio Palumbo : May be in the future. But today unfortunately, especially for myeloma, maybe different for other diseases, that is specially for myeloma we are substantially unable to predict which could be the outcome of our infusion, so.

Pat Killingsworth : Sure, sure, and I from your previous conversation I understand that you have access to Kyprolis, Carfilzomib

Dr. Antonio Palumbo : We don’t actually

Pat Killingsworth : Oh you don’t.

Dr. Antonio Palumbo : Yeah, that was one of the difference

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Pat Killingsworth : So you must not have access to Pamolidamide yet

Dr. Antonio Palumbo : Oh, Pamolidamide yes, Not yet Kyprolis.

Pat Killingsworth : Interesting! Here it was the other way round

Dr. Antonio Palumbo : Yeah, of course because this is sometimes may happen, because the criteria to approve those drugs sometimes do change from FDA to EMA and sometimes this is happening. So sometimes we have faster approval in Europe, sometimes it is exactly the opposite

Pat Killingsworth : Interesting! And here with Kyprolis.

Dr. Antonio Palumbo : Europe is on average it take longer.

Pat Killingsworth : Here with Kyprolis, they are finding that by increasing the dose is helping the efficacy, or whatever what the FDA approved, they are increasing that dose and they are increasing the efficacy, and then I listen to you say that you are going to once a week infusions. Is that at a higher dose or at the same dose

Dr. Antonio Palumbo : No, You are attaching an argument that is under investigation. So I cannot give today a clear answer, which is the issue.

Pat Killingsworth : Understood

Dr. Antonio Palumbo : If you compare 27 vs weekly, probably it is absolutely the same, even probably than better the weekly. If you start to use higher doses of twice weekly Crafilzomib, that is probably to be seen if they are absolutely identical and this is issue number 1 But issue number 2 is also another one. If you give weekly for a longer period of time, probably might be equal to twice weekly, because you cannot, you know, instead of giving to make you an example, 10 in one month, if you give 5 in two months, you basically might achieve the same efficacy. SO putting everything together, I would say today with 27 I would probably be comfortable to say that you are in the same range. For higher dose I think we need more data.

Pat Killingsworth : Of course, of course. Are you finding that the Kyprolis is helping some patients who become refractory to Velcade?

Dr. Antonio Palumbo : Absolutely yes. Kyprolis can be used in around I would say, 25% of resistant patient might have clinical benefit from the use of Kyprolis

Pat Killingsworth : Good, that is good news. And you still using Thalidomide often instead of Revlimid or is that starting to be substituted now?

Dr. Antonio Palumbo : Starting to be substituted and would be has been recently approved use of RD upfront, so I think we will substitute the MPT with RD finally

Pat Killingsworth : Sure

Dr. Antonio Palumbo : So Melphlan, Prednisone and Thalidomide with Len and Dex.

Pat Killingsworth : Interesting! Very helpful doctor, thank you.

Dr. Antonio Palumbo : Thank You.

Gary Petersen : Thank You Pat. Lizzy you got a couple more Questions and then we will go on to the listeners?

Lizzy Smith : Hi there, hi there. There seems to be quite a lot of debate on the role of maintenance therapy in myeloma, both short-term and indefinite. What are your thoughts on that?

Dr. Antonio Palumbo : My thoughts, let's put it this way – Continuous therapy is absolutely needed, because if you give a treatment for 6 months and you stop it, or you should give a treatment for 18 months, there is major difference. And continuous treatment is improving on a median, the remission duration of approximately one year to one year and a half, so the improvement is important and has been shown in every single study. Then not always these translate in survival improvement, because in some studies there is major survival improvement, in another its not. When we put together all the available studies there is also an advantage in survival. That is not so important as the remission duration, but there is an advantage in survival, so lets say a small advantage in survival, a major advantage in remission duration. The issue is should we give in until progression or should we give continuous therapy for 2 years. This is more troublesome and honestly today we do not have data to clearly show that until progression makes a major difference towards 2 years of maintenance. So, this is honestly a open question. Then the last statement I would do is continuous therapy is a plus, provided it is not creating any adverse event, provided it is not creating any toxicity. So in our clinic what we do, we deliver continuous treatment until progression, although we do not have major data to say that 2 years vs. until progression there is a plus for one choice vs the other. But we certainly stop every time there is an adverse event that might hamper the use of continuous therapy.

Lizzy Smith : Ok. Very interesting. Ok. So I go ahead and ask my last question?

Gary Petersen : Yeah, sure.

Lizzy Smith : Along those lines, What do you think are some of the more promising clinical trials that may lead to a cure or, at least, better long-term survival, for myeloma patient? Is there anything out there that, you think is really potentially ground breaking?

Dr. Antonio Palumbo : Well, there are many, because honestly today we have been using, I would say, if you want, there is short answer, the monoclonals. I think we are having now several new agents coming from Crafilzomib, Exazomib, what it will probably significantly change the treatment would be the use of monoclonals, and basically monoclonals antibodies that are reacting against the specific antigen present on the malignant plasma cell. They may be available pretty soon actually.

Gary Petersen : Fantastic. Now we will go on to the calls from our listeners. Priya would you see if anybody is online?

Priya Menon : Yes Gary, Listeners if you have a question for our panel, please press 1 on your keypad and I will bring you love to ask your question. Our first caller calling in from 7203716410 please ask your question, you are on air.

Gary Petersen : Next caller, or I will start with submitted questions

Priya Menon : Gary, because actually I think, they might have send in the questions to us already. Maybe we could just go questions, list of questions.

Gary Petersen : Doctor we have a number of submitted questions, without names, some are, first one, If IGG and M-spike are stable, but Kappa free light chains are going up, does it mean cancer is progressing?

Dr. Antonio Palumbo : If Kappa light chain is increasing the cancer is progressing. Of course it depends on the magnitude of increase so, if it is an important increase, Yes.

Gary Petersen : And what would an important increase be?

Dr. Antonio Palumbo : Important increase should be at least 30, 40, 50.

Gary Petersen : Ok. Ariane, writes – What is his view of using Velcade prophylactically after a SCT? Her husband (now aged 54 but 51 at diagnosis) had an autologous SCT in April 2013, which has left him with 5% to 7% myeloma on biopsy post the transplant. As this is only a partial response his consultant suggested Velcade prophylactically to increase the time before relapse – and he began this in September 2013 – but has made it clear that she does not know the efficacy rates.

Dr. Antonio Palumbo : This is very similar question to the previous one. Of Course you can have a continuous treatment with Lanolidamide or with Velcade, They are basically similar form that point of view. One is injection other is oral, but basically both are effective. The issue is the moment you are eager to more. If there is no toxicity, it is wiser to use the continuous treatment to keep the tumor under control. Otherwise if you stop, the probability of relapse will increase.

Gary Petersen : Ok. Would you suggest like adding Velcade, Dex to that or Thalidomide, Dex?

Dr. Antonio Palumbo : Well, this is honestly, we do not have evidence for this, that Dex. I would probably start in our practice with a single agent, eventually are the second agent if I am starting to see that something is moving otherwise, the other thing is absolutely stable, I would keep one agent approach.

Gary Petersen : IS that a cost consideration or is that a umm..

Dr. Antonio Palumbo : No, no, of course Dexamethasone is not adding any cost, so, it is not. No no no, I would use a single agent. Today we do not have a evidence that two agents are better than one as continuous therapy so.

Gary Petersen : How long should myeloma patients continue a treatment, such as Revlimid or Velcade? Would you talk a little about that?

Dr. Antonio Palumbo : This was exactly the question of before, more than how long I would grasp the concept – continue if no toxicity are coming first, with toxicity stop it. We do not have any data to say that 2 years vs until progression there is clash of one approach vs the other There is US studies ongoing, that will probably give us the answer, but today we do not have any data.

Gary Petersen : And now the next question is – When you are dealing with patients that have multiple prognostic indicators for high risk; in particular 17p, 1q21, and Fish 13 deletion – how do you determine the most appropriate treatment regimen?

Dr. Antonio Palumbo : My answer is unfortunately coming from a Bart Barlogie answer. I do not have any, today we do not have any specific treatment for high risk myeloma. We, of course do use dose intense treatment for these patients, but certainly today there is no treatment for high risk patients. So we certainly I would say, autologous transplantation, I would use Bortezomib induction autologous transplantation, Lenalidomide maintenance in the younger patients, and I would use once again, Bortezomib based induction, eventually followed by Lenalidomide or Bortezomib intervention in a non- transplant eligible patient.

Gary Petersen : Ok which answers the next one- What is the role of autologous SCT single, two, tandem, or none for high risk patients?

Dr. Antonio Palumbo : We use, of course for high risk auto transplant are indicated because we have certain giving, you know, for the high risk we give our best treatment, but we should basically the same to the standard risk, because the standard risk will do much better than high risk. So today, the answer is, these are dose intense treatment and not specific or peculiar regimen is indicated.

Gary Petersen : Ok, but you would use a tandem?

Dr. Antonio Palumbo : Yeah, Tandem for high risk.

Gary Petersen : Ok, do you use a lot of tandems then?

Dr. Antonio Palumbo : We use tandem in more patients

Gary Petersen : In all patients?

Dr. Antonio Palumbo : Yeah

Gary Petersen : Oh, Ok so, do you also use VDT PACE as well as Melphalan? In all patients?

Dr. Antonio Palumbo : No, no

Gary Petersen : They do that in Akansas, correct?

Dr. Antonio Palumbo : Yeah, yeah, yeah, No, no. We use VTD because it is reimbursed. VRD is not reimbursed, so we use VTD induction double transplant and VTD consolidation.

Gary Petersen : Ok, so PACE would not have been reimbursed

Dr. Antonio Palumbo : Yeah, is of course reimbursal issue. We need a glit in my country, well, all over Europe VRD is not reimbursed, so it cannot be used

Gary Petersen : Alright, does,ok and we talked, ok next one is really the same, but with a few other things in it, the 4-14 – Does ASCT have better outcomes for certain aberrations (T4:14, D17, T14:16, etc.)

Dr. Antonio Palumbo : No, The things are not much easier. First of all, do not pay too much attention to prognostic factors. On a single patient the prognostic factors are not so predictive, because we do not have biomarker that gives me a 95% probability to predict a given outcome. The prediction is around 30-35%, so we have one option out if two that is absolutely low as specificity in terms of predictors. Generally speaking the conclusion is of course that high risk do worse than standard risk, but on a single patient, still anything can happen.

Gary Petersen : What would your treatment strategy be for high risk patients, whose induction with RVD responded well, as it typically does, but relapse was quick, and treatments with CCD are not working (meaning poor or non- response enough to prevent going to first ASCT?

Dr. Antonio Palumbo : You see for this type of patient, first of all do a nice induction. And for them certainly VRD induction, double transplant, VRD consolidation, probably in this patient the maintenance should be a VRD cycle, every 2-3 months to keep the tumor under control with dose intense continuous therapy. So these should be done certainly in terms of induction to give the maximum and prolonged remission duration as long as possible. After relapse certainly once again the two option are – Kyprolis or Len or Cyclophosphamide

Gary Petersen : Ok. One thing we learned, not learned, but one of the things that Dr. Lonial from Emory mentioned, he had some pretty good results with a single transplant but you know with high risk disease, and I can't remember the induction, but he is…

Dr. Antonio Palumbo : He is using exactly the approach I just mentioned before – VRD transplant, VRD and keep going with the same scheme. I have to make a..Today honestly we use that tandem, there is no evidence that tandem is superior to single. There are ongoing studies that are evaluating this issue, but

honestly, I cannot say that 2 is better than 1. Today no one can say 2 is better than 1 or 1 is better than 2.

Gary Petersen : Ok. His research would indicate that, or he was thinking, he just says a supposition on his part, and the supposition was that the genetics of the high risk patients is unstable and Melphalan can aggravate that, and so if you had higher doses of Melphalan which is a second transplant could be more negative than positive

Dr. Antonio Palumbo : Difference between the Europe and US. We rely more on the evidence coming from study that on personal opinion. Generally speaking the evidence today is that if you give autologous transplantation is high risk patient is better than if you don't give it.

Gary Petersen : And that is based on clinical trial?

Dr. Antonio Palumbo : We do have this, Yes, we do have this evidence from trials.

Gary Petersen : And I know you have got tremendous amount of experience in Clinical trial, you have tried about everything in Italy. Does the European perspective of myeloma treatment emphasize more on 'cure of myeloma' using intensive multi-drug strategy aiming at complete response or more on 'control' of myeloma aimed at Quality of life?

Dr. Antonio Palumbo : The cure today, let's say can be stand between 15-25%, so we stand more for control.

Gary Petersen : Alright. Is early therapy in newly diagnosed MM or Smoldering MM patients more advantageous or more disadvantageous according to you?

Dr. Antonio Palumbo : Early is always more advantageous.

Gary Petersen : More advantageous OK. Could you give your opinion, and you already have on monoclonal antibodies in treatment, and I would say, you know, would it be single agent, it would be in combination with transplant.

Dr. Antonio Palumbo : Would be a combination, would be a combination with. We will basically add the monoclonal to current treatment scheme.

Gary Petersen : You would add it to Carfilzomib?

Dr. Antonio Palumbo : Yeah, Yeah, , the future would be, basically we will add monoclonals to what we are using today, so RD, VD, VRD and CRD and so on.

Gary Petersen : Ok. Fantastic. Priya anybody online?

Priya Menon : Inaudible

Gary Petersen : Ok. Any last questions for our Dr. Palumbo from the Panel?

Lizzy Smith : Hi Gary, can you hear me. Ok I do have a followup, So, Dr.Palumbo, the perspective of a patient who is on long term therapy or maintenance therapy for example, what are the risks of becoming immune to those drugs, so that they no longer work. So, its perhaps abetter option to may be go, if a patient is in remission to go off of the treatment so that when a patient relapses, those drugs are more effective?

Dr. Antonio Palumbo : No, The balance is, if you do not do anything, the risk of relapse is 70%, I am giving just number to give you ideas. If you give a continuous treatment risk of more aggressive disease is 20% So it is always true that giving a continuous treatment, you going to chemo-resistance, but is much more

prominent the risk of not doing anything and do have an aggressive relapse. So, the balance is between the continuous therapy that keep the tumors under control and avoid the creation of new genetic mutation that might increase the aggressiveness of the tumor, and this is much more prominent, in comparison to the risk of having anyway a genetic mutation that will make a tumor more aggressive.

Lizzy Smith : Ok. That is a very good reason to stay on maintenance therapy. Thank you.

Gary Petersen : And thank you for joining us Lizzy

Lizzy Smith : My pleasure.

Gary Petersen : You just jump right in there like you were a pro.

Lizzy Smith : Unfortunately.

Gary Petersen : And Dr. Palumbo, as I stated before, I put a list together who I thought were the great eight of myeloma specialist in the world and you are on my list. Also very highly rated by Pat, who is very very much part of the patient advocate population. So, we thank you so much for the time that you spent with us and for your insights on the differences, and obviously you guys in Europe do more with less, and you do more with less because you have less than half of the cost per patient and you do more because you don't get the drug as quickly as we do So, the fact that your average life expectancy is good or better than that in the US, speaks volumes for your efforts. So thank you so much.

Dr. Antonio Palumbo : Thank You for everything. Thank you for the invitation. Thank you very much.

Priya Menon : Thank you. Thank you Gary. Dr. Palumbo its been great listening to you. Lizzy, Pat and Jack, Thanks a lot. Please join us again for our next myeloma episode where we would be discussing Early treatment of myeloma with Dr. Irene Bobrial on Feb 16th at 6PM eastern time. The link for today's broadcast will be shared with all participants. Please visit curetalks.com to register for our shows. Until then thank you.

Gary Petersen : Thanks again doctor

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