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# Acute lymphoblastic leukaemia in childhood and adolescence (held in collaboration with SIOPe)

**Dr Rizzari:** Thank you. Good afternoon and good evening to all the people listening to this session. So, we start with the topic which is Acute lymphoblastic leukaemia in childhood and adolescence. I will immediately start with some definitions because I think this is the introductory part. Acute lymphoblastic leukemia is a tumor, is a cancer of the blood and consists of the uncontrolled proliferation of immature blood cells of different immunological subtypes. This is a cancer; this is a deadly disease. This will lead the patient to death. The disorder starts in the bone marrow, where normally are produced the white blood cells count, where red blood cells and the platelets and the leukemic cells will take over the production of cells in the bone marrow. There are different characteristics as in every single tumor, but these diseases particularly well-studied and has been worst in the past. And so, we know very much about these cells. One of the major factors for avoiding relapse or insuring outcome and cure is response to treatment. And we will try to see how this happens. This is just a cartoon showing that, on the left side of the cartoon, the normal evolution of the cells coming from the pluripotent stem cell. And you may see that on the left hand side, and on the top of the cartoon, you may see that from the lymphoid stem cell will come out the B-cells and T-cells, which are basically the two main types of lymphocytes working very beautifully, normally, for defending us from the problems coming from outside of our body. On the right hand side, you will see how this can change in terms of production of lymphoid blast. Acute lymphoblastic leukemia is a disease, which is typical in childhood. And we saw, as pediatricians, we see the vast majority of acute lymphoblastic leukemia seen in the human kind I would say. There is a peak in terms of years and age distribution between three and four, five years old, there is a male predominance. This is... You may see in the cartoon the difference between the peak of ALL you see, which is clearly between the age of two and six, and, this is conversely the incidents of acute myeloid leukemia in childhood. And you see that throughout the different years, you cannot see any difference or any peak. There is a male predominance, girl to boy ratio is 1:1.2. Inside the leukemic cells, there are, of course, chromosomes, there are abnormalities in these chromosomes. These are malignant cells and so, some of these cells will have a number of chromosomes which is reduced; in this case it's called, on the left hand side, the hypodiploidy. It can be augmented you see, the hyperdiploidy can be translocated or be duplicated some chromosomes. So, you may see the T (4;11) and the Ph+ which is a translocation (9;22), the trisomy 4,10,17 and the translocation (12;21). On the right hand side of this slide, you see the three major cytogenetic factors, which have a favorable and on the left hand side there you see the factors cytogenetic factors, which are associated with the non-favorable prognosis. These cells are different in terms of maturation and also of the surface. From the left hand side, you see the T lymphocyte or T blast, and on the right hand side, the B lymphoblast. And you see all these numbers with the CD, which means Cluster of Differentiation on the external part of the cells. There are

some of these signals, or this cluster of differentiation, and these will give to the cell, to the leukemic cell a further and a specific name. And also, this reflects the maturation of the cell. As we had said before, we had simplified before the Cytogenetic alterations which can be at a favorable or non-favorable prognosis. This is a classical cake, where you see several pieces, several slices which represents the percentage of the numerous alterations. It is calculated that the vast majority of leukemic B cells will bear some kind of cytogenetic alterations. And here, you will see the different incidents. Acute lymphoblastic leukaemia in childhood can be associated with some diseases, especially some genetic diseases like, you see in the left hand side and then the top of this slide, the Neurofibromatosis, Ataxic Telangiectasia, Li-Fraumeni Syndrome, Fanconi Anemia, Bloom Syndrome. These are all genetic diseases, which are associated with acute lymphoblastic leukaemia. On the right hand side, you see the different, some of these cytogenetic abnormalities and it is important to study these, because, for some of these diseases, you may have some targets and you can have also have some specific treatments. For example, the translocation (9;22) so called also Philadelphia positive, you may know that there is a class of drugs, which is called the tyrosine kinase inhibitors, which is beautifully working on these abnormalities and contributing in a very important way to the treatment and cure of the patients. In general, the treatment for a pediatric ALL is outlined in the lower part of this slide. There is an induction which means basically using three or four drugs, especially, vincristine, steroid, asparaginase, intrathecal chemotherapy, to obtain the reduction of blast cells in the bone marrow and thereafter, the complete remission achieved. Complete remission means basically that the patient is getting the normal counts after four to five weeks. Thereafter, there will be additional phases and there is a delayed intensification, which is considered a very important of this treatment. And thereafter, there is the maintenance. Overall, the treatment in general lasts about two years for all children who do not undergo any bone marrow transplantation procedure. At this point, there should be some slides to show you that you may ask questions, and so, I don't see them, but I can tell them. You can post questions just using the specific buttons you have on your screens.

**Dr Attarbaschi:** Carmelo, may I ask you a question? What is your opinion about the anthracycline in the induction part?

**Dr Rizzari:** Well, this is a very good question because anthracycline is a very good class of drugs, for some of these drugs, for these drugs, these drugs have been associated with cardiac toxicity and are very potent immunosuppressants. So, there is a price to pay for the use of these drugs. For some patients, these drugs can also be spared in induction. There are protocols where these drugs are not used, but, for the vast majority of the protocol currently, the anthracyclines are used, I would say, for at least a 75 to 80% of the patients.

**Dr Attarbaschi:** Thank you.

**Dr Rizzari:** Well, in this slide you see the, on the left hand side, the Germline, which is the Host Genome, which is important for systemic pharmacokinetics, drug toxicity, so, on the normal tissues, which means, basically, that when you administer a drug to the patient, independently of the underlying disease, he will have interaction with the drug and this will lead to some effects. So, these effects are, of course, for the chemotherapy drugs, killing of blastic cells, but also giving some side effects to the other parts of the book. Then there are the somatic alterations which basically refer to the cancer genome. And for this part, there can be a completely different interaction with the disease, with the chemotherapy drugs administered. This is something that I like to show because, basically, gives the opportunity to understand how much it's possible to have children cured from acute lymphoblastic leukaemia. In this part of the graph, you see in this cartoon, you see, these three bars refer to acute lymphoblastic leukaemia. And, basically, these numbers, these bars are of different length, because depend on when it is seen the cohort. In other words, basically, in some of these patients in the first one or two years will be almost completely out of the disease, but, thereafter, there will be some patients relapsing. So, after the end, the numbers are at five years of patient's cures will be around 80%. Here, are coming the slide. So, you can ask questions and send comments at any time. So, as I

said before, approximately 80% event-free survival five years can be achieved in a general population. In general, how can we stratify patients? There are two main ways. One is the National Cancer Institute risk grouping, which is based on upfront criteria, which is white blood cell count, age, for example, versus the use of late criteria, such as the response and in general, nowadays this is getting more and more relevance in terms of stratifications. Of course, there will be also the new molecular subgroups, as I said before, the Ph-like, or BCR/ABL-like, C-ALL and MPAL which are phenotypes or diseases which have a different, or a very similar immunophenotypic behavior to the classical Philadelphia chromosome positive ALL, or the myeloid leukaemia. But these subgroups, at the present time, are still under very close evaluation for becoming established risk factors. And the response is very important. There are possible possibilities to evaluate the response after a few days of steroids. There is the possibility to evaluate the morphological CR after the first four to five weeks, there is the MRD detection, we will see them in a moment, how much is nowadays important the MRD detection. Translation of novel molecular findings into improved treatment outcome is under investigation as I said before. So, in other words, after the present time to stratify patients, we very much rely on some established cytogenetics or molecular genetics alterations and to the response. These are the very strong predictors of outcome, thereafter, there are also novel treatment approaches based on immunotherapy. We will just attach this because this is the frontier of the treatment. And the first of all, we wanted to touch the established treatments. So, again, treatment-response is the result of these different four areas: the host, the leukemic cell, the micro-environment, and the therapy. So, this is very important to be remembered. So, the disease outcome does not depend on the type of treatment, it depends on the patient's characteristics, it depends on the leukaemia characteristics. It depends also in the interactions with the micro-environment. This is very important, but this is not new because, human being is the mix of all these things for almost, or every disease. What I show you here is the acute lymphoblastic leukaemia BFM, which is the acromial Berlin-Frankfurt-Muenster Backbone. What does it mean? That this is in one consortium, which is a ??country?? named the IAPHO, which stands for Italian Association for Pediatric Hematology Oncology and BFM which is Berlin-Frankfurt-Muenster. So, basically, German, Austria, and Switzerland tradition in terms of chemotherapy treatment, is the main scheme used since I would say almost 30 years or 40 years in the treatment with progressive refinements and you see the blue part is the induction. The yellow is the consolidation. The red one is the delayed intensification. Then there is the light blue maintenance. This is an established, very well-established treatment. The same results can be obtained with some differences, but basically the drugs, the timelines and the phases nowadays are pretty similar. Some protocols have more of one drug or less than one drug, but overall, the goal is during induction obtain the complete remission, then consolidate, then re-induct, reduce and then maintenance. This treatment, as it is, will cure at least 80% of unselected cohort of patients. And these are the numbers, in this cartoon you may see that there are a lot of acronyms on the left-hand side, and you see here of DCOG, UK. These are all international groups and just to show you that the five-year overall survival is nowadays 98, 90 to 91%. So, after five years, 91% over your patients will survive to the disease. And this is the five-year cumulative incidence of any event. Most of these events will be relapsed. So, the main goal of the treatment for acute lymphoblastic leukaemia in childhood is to avoid the relapse. Because, if you avoid the relapse, you will cure more patients. Remember, that you can ask questions. Age is a factor, particularly important. To be consistent with the presentation, I thought that I could have shown some slides showing the importance of age. You may know that the pediatric age spans from zero to 18 years old. So, but when you treat the patients in a range of four to seven to eight years is completely different than treating an adolescent of 14, 15 or 16 years. In these patients, there are, a therapeutic approach, which have to be modulated in respect of the children. One additional aspect very important you will see here the GIMEMA which is the Adult Hematology group in Italy and the AIEOP which is the Pediatric Hematology group in Italy. You see that if you just split the age cohorts, you see that the green bars represent the ETVC/RUNX which is the translocation 10,12,21, which is a good favorable prognosis. But when you go and go for all the patients, this translocation almost completely disappears. Conversely, if you look at the BCR/ABL, which are the purple bars, you see that there is almost no patient in the pediatric age. This is calculated about 2 to 3%, but in the adult age, this is much,

much higher. And this gives the idea of how much different can be treating the same disease in different ages. And the different ages also have a lot of differences in terms of toxicity. Here in this cartoon, you may see that out of 1,076 patients, published by the Nordic countries group, which is the NOPHO-ALL 2008. And if you just list on the left hand side, the major complications, you see that from one to nine, 10 to 14, 15 to 17, 18 to 26, et cetera, et cetera, you see that the differences are striking. For example, look at the liver dysfunction. It is 3% and it increases to 4.5% in the older age. Thrombosis is 3% in childhood and this is 16% in older patients. Seizures, the PRES, some are mainly seen in children and almost never seen in adults. The fungal infections, 6.9% in children, 19% in adults. So, it is very important, when you treat a patient, you have to take care of the patients according to the disease, according to the characteristics, but according also to the age. You have to be very careful because the best treatment is not the one written in the protocol, the best treatment is the one written in the protocol modulated according to what you know is the fragility of your patients. And this is clear, you see here, the event-free survival. So, difference in terms of capacity to resist to the side effects of chemotherapy clearly is reflected also in the outcome. So, you see here four different events, free-survival curves, showing that if you take the different cohorts with the progression of the age, you will find different outcomes. So, this is related to the characteristics of the disease, to the sensitivity of the disease, but also to the possibility to deliver to different groups of patients, the same chemotherapy protocol. Here you see the AIEOP-BFM ALL 2000 protocol which is, as represented, the trial treating 4,730 patients. We have subdivided one to nine years, versus 10 to 14 or 15 to 17. And you may see that for example, the resistant diseases are .1, .1, 1.4. You may see that the death in CR is .7 after chemo; 1.7, 4.6, and the remission rate is 98.9 years, 97.5, 96.8. Now, it seems a very small difference, but, as a pediatrician, we are used to have almost each single patient remissioned after induction. For an adolescent this is very much possible, but you still see some patients resisting it. Alive in CCR, 88.9%, 81.7%, 75%. So, you'll lose about 15 points from the group, less than 10 in the group of 15 to 17 years old. If there are any questions, please do not hesitate to do so. Minimal residual diseases and I would say that at the present time, one of the most important prognostic factors. Minimal Residual Disease is well-known as a factor since the 90s. This is the first paper published by Jacques van Dongen and the international group of the AIEOP-BFM consortium showing that, you see, that when you study at time points one and two, this is a small number of patients, but this I can tell you that is completely confirmed in thousands of patients. If you take .1 and .2, and you just measure the minimal residual disease with a specific way, which is this receptor of the immunoglobulin rearrangements, you may beautifully subdivide the group of ALL in three subgroups: the low risk, which is a negative one, negative two, intermediate which is positive one and negative two. And the high-risk group, which is positive one and positive two. When I tell this to some residents, or students, or younger oncologist, I always tell the same thing, it's exactly like bronchopneumonia. When you get very well after a few days of antibiotics, you will have a very beautiful outcome. When you don't have this response, you are going to have a long interaction with the infectious disease. The same is for leukaemia. If the disease is very, you know, responding very well, already at point 1, outcome is, almost for each single patient, the cure, which is not the case if we have the opposite. So, when you do not respond adequately at point 1 and 2, the outcome is very dismal. And this is very important, because for these patients you can spare some chemotherapy intensity, and for these patients you can increase and even use the bone marrow transplantation as a salvage process, procedure. You see. These are the percentage of patients, 4% of relapses here, 42% of relapses here, 54% of relapses here. And this is exactly the subdivision in the MRD ALL 2000. So, just to go back, these are patients investigated back in the 90s, and these are patients who have applied these criteria and you see that there is a very beautiful dissection of the cohort in three groups. The highest group, of course, is not that bad because there has been an intensification of the treatment, and some of these patients have been salvaged with the bone marrow transplantation. And here you will see that if you use a tool which is called the Flow Cytometry, which is exactly the way to investigate the surface and the phenotype of these cells. Very earlier, at day 15, which means at this point, the patients have received just two weeks of steroids. One vincristine, one ??dexamethasone??, one pegylated asparaginase, you may see that on day 15. And if you follow these patients, patients with a very good response already on day 15,

have a very good outcome in the range of 93%. If this is not very good, which is less than 10%, but more than .1%, you will have 79%. And if you have more than 10% of blasts, day 15 measured by the flow cytometry the outcome is very bad. This is just to confirm the concept. The response to the treatment is very important. So, we have seen the cytogenetics, we have seen the age, we have seen now the response in terms of immunophenotyping and flow cytometry. There are no questions. So, go ahead. Childhood and adolescence, acute lymphoblastic leukemia, steroids and immunophenotype. So, very briefly, I have a series of curves. So, dexamethasone and prednisone. This is a randomized study. You see that just changing the steroid during induction can make the difference. Five points of difference, dexamethasone versus prednisone. Thereafter, when these patients were relapsing, they were rescued with the second line treatment. So, the survival is exactly super impossible. The T ALL, according to the steroids, can have a different behavior. If you treat the patient with T ALL with prednisone, you have a worse response in terms of outcome, in respect of treating with dexamethasone. The same is when the person would respond by first random. So, dexamethasone goes down, the prednisone goes up and so on. I will go over to the protocol 2009. And this protocol, you see, after the present time, in this protocol, which started in 2009, has a dexamethasone, which is D and that's prednisone for the vast majority of the additional patients. And then there are additional questions. So, for example, this study was very much focused on pegylated asparaginase given in intermediate-risk patients and also in high-risk patients during the phase one-B. And so, just to say you, that the outcome of the 2009 is excellent. As we started, you remember, with the 90.8, this is 91.6 survival, the event-Free Survival is 83.1%. So, this is absolutely an excellent result. But if you look at it at 2000 protocol, which is the previous one, we had the 90.5 and 82.1. So, we changed the steroids, we asked new questions, but overall, the response is more or less the same. The gain is very, very small. Just a brief touch on immunotherapy, because this is something that all the people are talking about. And, you will be asked an opinion about Immunotherapy. Why do we think we talk about immunotherapy? We talked about immunotherapy because chemotherapy has a price, as we said before, has a price in terms of acute and also long-term toxicity. I will not go into the details, but just will tell you that there are encouraging new drugs which can be used for targeting some specific parts of the leukemic cell. One of these is the so-called Bi-specific antibody called Blinatumomab, which is able to put together the CD3 of the T normal lymphocyte with the CD 19, you see here, of the leukemic blast. This is a dream. This is a special weapon, which is able to put together the normal T lymphocytes with the leukemic blast and allowing the killing of the cell. And, just to tell you that the progression, the science in this field is, you know, progressing but we are nowadays in 2020, but the studies I've shown you started in 1990. So, it's already 30 years and nowadays in many countries, participating in the AIEOP-BFM ALL consortium, the random is on the use of blinatumomab in frontline patients. So, you'll see here, medium-risk and high-risk patients. Why this? Because the chemotherapy is very effective, but has a weight. And we were trying to maintain the outcomes with less burden of the treatment. So, I am almost finished, just a few remarks. Childhood ALL is a rare disease. I can tell you that, for example, in Italy, there are 60 million people, there are 12-13 millions of children and every year we see about 400-450 new cases. Remember, that the childhood ALL is the most frequent cancer in childhood. And remember also the cancer in childhood is the first cause of death, still, the cancer, still, for children after the accidents. But ALL is the history of great progress. Nowadays, thinking that 90% of children can be cured with mainly the first line of treatment is an extraordinary advance. But within ALL there are differences. There are differences which have to be taken into account. It is important to have adequate teams, clinical skills, organization resources, and we have to take care also of the late complications. So, the attempt is maintain the excellent cure-rates improve where it is possible to improve, but without harming the patients and without increasing the burden of the treatment. Immunotherapies and cellular therapies, I have no time to discuss with you about CAR-T cells, which is very much, you know, reported in the news and also in the scientific symposium. These are at the forefront. So, we hope that immunotherapies and cellular therapies will even contribute to cure the remaining 10% of our patients who are not cured. But long-term survivors, which is, I mean, are those coming from the last 30 years, who sometimes have problems and the need to be followed-up, I think that these patients deserve a plan for follow-up very, very important. I have a finished here. I think I am almost in time.

This is the group of people working in Monza and we work all together and this is our, you know, our group and we are very proud of that. So, I just wanted to maybe ask Andishe if he wants to interact with the audience and with myself.

**Dr Attarbaschi:** Thank you Carmelo for this very, very nice overview on the most common cancer, into children. And there are lots of people in the chat. Are there any questions or remarks to what Carmelo has told us today in the evening? Perhaps, before the people start writing down the questions, I could ask a question to you. When I look back to 1970, when we had the first BFN trial just in West Berlin, patients only got protocol 1A, protocol 1B, cranial irradiation and maintenance. I think about 80 or 75 patients were included in this trial and event-free survival, long-term event free survival was around 50%. Do you think that we can ever identify patients who can be cured with a very short chemotherapy and maintenance? Or do you think this is impossible?

**Dr Rizzari:** Well, this is a very good question Andishe. At that time, the cranial radiotherapy was doing a part of the job, but, you know, and, unfortunately, some of our patients have experienced the late effects and even second cranial tumors. So, it is very difficult to dissect that which patients can be cured with a low level of chemotherapy. Certainly, we don't want radiotherapy, some protocols have been able to reduce, and among these also the AIEOP-BFM ALL 2017, where the number of patients is very, very small, which will be radiated. The point is that when you reduce the risk of the treatment, even if you have the minimal residual disease as a tool to identify patients with very good outcomes. We have seen experiences showing that when you step-back in the intensity of the treatment, immediately, you pay with some additional relapses. I am completely convinced that a part of these patients can be cured with very low level of chemotherapy, but this philosophy is hardly applicable nowadays, because, well, [Audio Not Clear] which is one of the fathers of the leukemia in childhood always was saying, the first objective is to avoid the relapses. Relapses sometimes are easy to create, because are late, are still sensitive but second line treatment is a nightmare for the patient and for the family. So, I think that the answer to your question is, yes, there are patients that could be cured. Identifying these patients is very difficult and at the present time I would say that the vast majority of patients even receiving an intensive treatment will come back to a normal life without absolutely no side effects on the long-run.

**Dr Attarbaschi:** Yeah, and thank you very much for this clear answer and I completely agree with you. It's also my personal thought. Any other questions in the chat? The number of attendees has increased, but no question at the moment, perhaps, I have one last question. When I look at all the survival rates that you have very nicely shown, again, I see that dexamethasone during induction therapy was something which really changed survival-rates by reducing the number of relapses by 1/3. Do you think that the time for testing dexamethasone using dexamethasone induction has vanished completely, or what is your thought still about dexamethasone? We are using it for T ALL you notice in our own trial. But for B-ALL we're not using it. Do you think it will ever find a place again, or not?

**Dr Rizzari:** Well, we have to think that dexamethasone is already administered to our patients, I mean, protocol two or protocol three. So, it is not exactly the same amount as in induction. The experience in the AIEOP-BFM-BFM at 2000 study was important. And you're right emphasizing the availability, the possibility to have at least a five more percent of patients cured overall, because there are subgroups which are even different with a drug, which is given in induction. So, this is biologically very intriguing. So, you administer it. Just change a simple drug during induction and the curbs divert two years later. This is extremely interesting from the biological point of view. The point was that dexamethasone had to be used at a very high dosage and this determined a lot of problems, infectious problems, especially for the fragile population which is the adolescence, fragile in terms of toxicity. And in additional, some of these patients experienced fungal diseases. They had bacterial sepsis, and they also experienced osteonecrosis. So, since our outcome at the end, was in terms of survival, the same among the two groups, we decided not to go for dexamethasone again for the whole population. But you are right. It is possible. There are some other groups trying to use

dexamethasone at a lower-dosage, pretending that a lower dosage will make the same good work on the leukemic blast, but less harm to the mucosa and to the patient. It is not granted, but the only category which is taking a greater advantage from dexamethasone induction is a specific subgroup of patients, the so-called the patients-good responders with the ALL. I would say, I am happy to spare my patients from dexamethasone induction, because I think that, after the present time, with immunotherapy and the advances in this field, I think that patients will do fairly, not very, well, have new and maybe more targeted opportunities to solve the problem of the resistance or of the bad prognostic factors in their diseases. So, dexamethasone is a part of the story of acute lymphoblastic leukemia. Personally, I think that in the future, there will not be that much space for dexamethasone to solve the problems of our kids.

**Dr Attarbaschi:** Thanks for sharing your opinion on this aspect of ALL therapy So, I think if there are no further questions within the audience, I would like to thank you Carmelo. I enjoyed your talk very much.

**Dr Rizzari:** Yes. Thank you.

**Dr Attarbaschi:** I was happy to be a discussant, and I hope ...

**Dr Rizzari:** That was very interesting questions and, I hope that the audience and the people who had the patience to listen to this presentation, can take home some messages, which are very important, and maybe this will help them in their daily activities and maybe also their patients.

**Dr Attarbaschi:** I'm sure about this and it's a recorded session. So, I hope that people who have not time today to come to listen to you, will listen to it afterwards. So, thank you for the presentation and nice evening with you. And goodbye for everyone.

**Dr Rizzari:** Thank you very much.

**Dr Attarbaschi:** Bye-bye. Ciao.

**Dr Rizzari:** Ciao, ciao. Bye-bye.