Raisa Gorbacheva Memorial Lecture

given at the Symposium on Hematopoietic Stem Cell Transplantation on the
110th anniversary of the Saint Petersburg State Medical I. Pavlov University,
which took place on 21–22 September 2007

Treatment of Acute Myeloid Leukemia: Present Status and New Directions

Thomas Büchner, MD PhD

Professor of Medicine and Hematology
University of Münster, Germany
buechnr@uni-muenster.de

Prof. Yaitsky, Rector of the University, Prof. Roumiantsev, Prof. Afanasyev, Prof. Zander, Ladies and Gentlemen,

Dear Prof. Afanasyev,

My congratulations for your important achievement, and for the great day you had yesterday with the opening of the new clinic, the Raisa Gorbacheva Memorial Institute of Children Hematology and Transplantation, also for your research team, for all your cooperators, supporters, and sponsors. You do not make much noise, but we all know what you created during the past two years. Thank you, and good wishes for a good cooperation in the future.

Raisa Gorbacheva, 1999

Ladies and Gentlemen, were are assembled here in memory of Raisa Gorbacheva.

In August 1999, I received a letter from Prof. Roumiantsev and Prof. Vladimirskaya from the Research Institute of Paediatric Haematology in Moscow. The letter said: „Raisa Gorbacheva was the first person in Russia who, in 1991, has supported us in our struggle with acute leukemia in children. She was the first initiator of the foundation of the International Association *Hematologists of the World for Children*. The department of bone marrow transplantation in our institute was in fact built only because of the support of the Gorbachev family and of Raisa Maximowna personally. During these 9 years, Raisa and the Gorbachev family helped us not only morally, but also financially, with the royalties from book publications authors by both herself and her husband, and of course by the Peace Nobel Prize award sum.“

I know that this support is continuing until today, as we saw yesterday.

In 1986, the Gorbachevs side by side visited East Berlin. And during the following years, Mikhail Gorbachev pursued the idea of “Glasnost” and “Perestrojka”, that turned out to eventually cause a revolution in our two countries, in Europe and in the world.

Three years later, in 1989, I got my first opportunity to visit your country by an invitation to a hematology symposium to be held at “Pushkinskie Gory”.

1989 Symposium in Pushkinskie Gory on Acute Leukemia and Lymphoproliferative Diseases

We started our trip in Moscow by bus and we had two excellent Russian piano-players in our group who played Chopin for us and Mussorgsky at the house of Mussorgsky‘s which we visited before we continued to Pushkinskie Gory.

There we had a symposium on Acute Leukemia and Lymphoproliferative Diseases. I was asked to give a lecture on Acute Myeloid Leukemia.

I started this lecture by thanking the organisers for inviting me, although I was a German. But they accepted this German and they gave us their friendship.

On the left photo you can see Andrej Vorobiev, actually one of our teachers.

Andrej Vorobiev, Mrs Büchner, Don Thomas (from left to right)

Boris Afanasyev, 1989, another important teacher

Let us now talk about Acute Myeloid Leukemia (AML), about the disease itself and the problems linked to the disease. AML is characterised by a bone marrow tightly packed with leukemic cells. All cells which produce normal blood cells have disappeared.

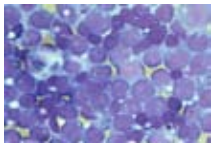


Image 1. AML bone marrow

When we remove the leukemic cell burden by chemotherapy until bone marrow gets empty and does not contain any blood forming cells, only some tissue cells are left.

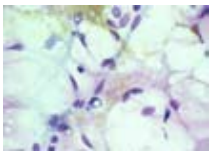


Image 2. AML bone marrow, aplasia after chemotherapy

This is a chance for a normal cell population to recover so that a patient can go into a complete remission where she or he feels well and we are not able to detect leukemic cells any more, and the patient may even be cured, if not relapsing later.

In 1969, all patients still died within two years, and half of the patients even died within the first five months. This was the pre-chemotherapy era, again confirming AML to be a most aggressive and dreadful disease.

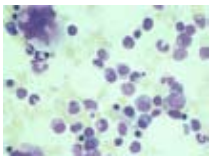


Image 3. AML bone marrow, complete remission after chemotherapy

The first of the two tables below shows the results in complete remissions (CR) and 4-5-year continuous complete remissions (CCR) in multicenter randomized trials for younger patients, and the second table represents the results for older patients.

Table 1. Complete remissions (CR) and 4–5-year continuous complete remissions (CCR) in multicenter randomized trials in the order of patients age: Younger patients

Publication	Age	No. of patients	% CR	% CCR at 4–5 Y
Hann et al. 1997 Burnett et a. 1998	0–55	1857	82	42
Mandelli et al. 1992	15–55	448	68	24
Cassileth et al. 1998	16–55	740	70	35–43
Rai et al. 1981	0–60	247	36-59	22 (not age specific)
Yates et al. 1982	1–60	427	57-72	not given
Büchner et al. 1985	16–60	255	68	8–24
Rees at al. 1986	0–60	740	73	18
Hayat et al. 1986	10–60	257	66	17 (not age specific)
Zittoun et al. 1995	11–59	941	66	44
Preisler et al. 1987	14–60	564	65	17
Hansen et al. 1991	17–60	135	60	34
Dillman et al. 1991	15–60	226	69	10 (not age specific)
Cassileth et al. 1992	15–60	376	71	16–27 (not age specific)
Mayer et al. 1994	16–60	742	71	24–44
Bishop et al. 1996	15–60	301	73	23–41
Weick et al. 1996	< 65	665	54	19
Büchner et al. 1999	16–60	725	68	32
Büchner et al. 2003	16–60	535	74	34
Löwenberg et al. 2003	18–60	640	81	39
Büchner et al. 2006	16–60	840	70	45

Table 2. Complete remissions (CR) and 4–5-year continuous complete remissions (CCR) in multicenter randomized trials in the order of patients age: Older patients

Publication	Age	No. of patients	% CR	% CCR at 4–5 Y
Hayat et al. 1986	60–65	30	47	no age specific data
Hansen et al. 1991	60–65	39	46	30
Cassileth et al. 1992	60–65	73	52	no age specific data
Rowe et al. 1995	55–70	117	61	not given
Witz et al. 1998	55–75	132	62	23
Goldstone et al. 2001	56–80	1311	50–62	15–18
Anderson et al. 2002	56–84	328	38	15
Rai et al. 1981	60+	105	16–45	no age specific data
Yates et al. 1982	60–84	226	31–47	not given
Büchner et al. 1985	60–78	79	39	0–28
Büchner et al. 2003	60–82	297	60	13
Rees et al. 1986	60–83	305	48	9
Preisler et al. 1987	60+	104	41	17
Dillman et al. 1991	60–83	100	41	no age specific data
Mayer et al. 1994	60–86	346	47	15
Stone et al. 1995	60+	388	53	13
Büchner et al. 1997	60+	340	42–54	22
Dombret et al. 1995	65+	172	47–70	not given
Rees et al. 1996	1–79	923	63	26 (not age specific)
Bishop et al. 1990	15–70	264	58	14–37 (not age specific)
Löwenberg et al. 1998	60–88	489	38–47	7–13
Rowe et al. 2004	56–86	348	42	4
Büchner et al. 2006	60–85	930	53	16

In 1981 and the following years, many reports in multicenter randomized trials were published. And we have to go into all these publications in order to learn our lessons. This is what those 20.000 patients have given us.

Mean percent complete remissions in 31 randomized multicenter trials and 19.882 patients increased over time from 66% to 72% in younger patients, and similarly from 42% to 51% in older patients.

Table 3. Mean percent complete remissions in 31 randomized multicenter trials and 19 882 patients

Age (years)	Year of publication	
	1980–1990	1991-2006
< 60	66%	72%
60+	42%	51%

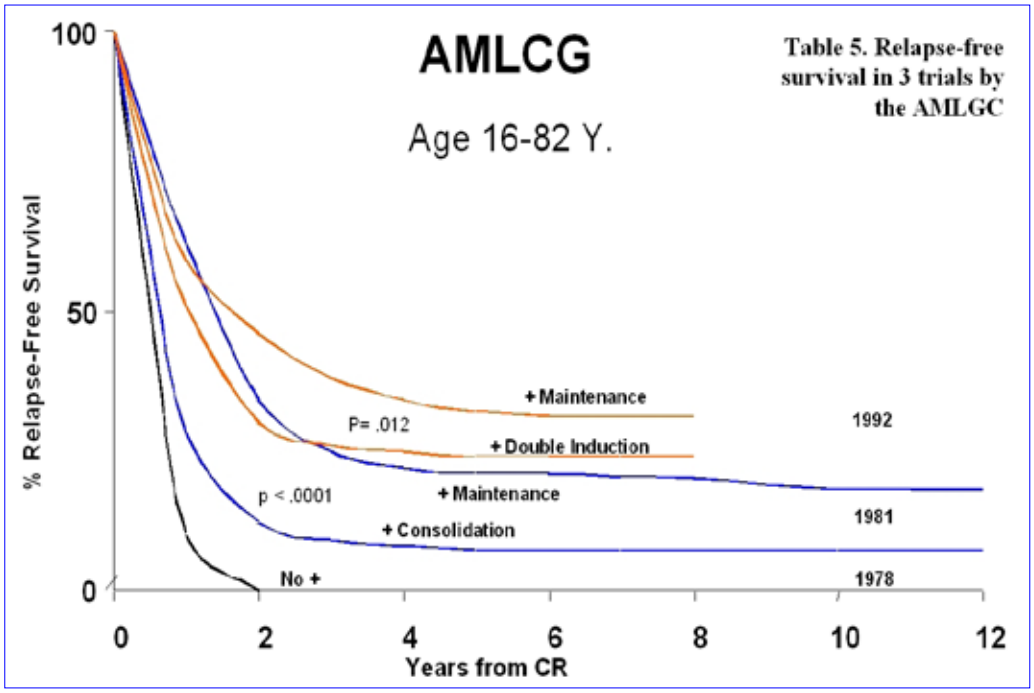
Table 4. Mean percent continuous complete remissions at 4–5 years in 31 randomized multicenter trials

Age (years)	Year of publication	
	1980–1990	1991–2006
< 60	17%	34%
60+	11%	15%

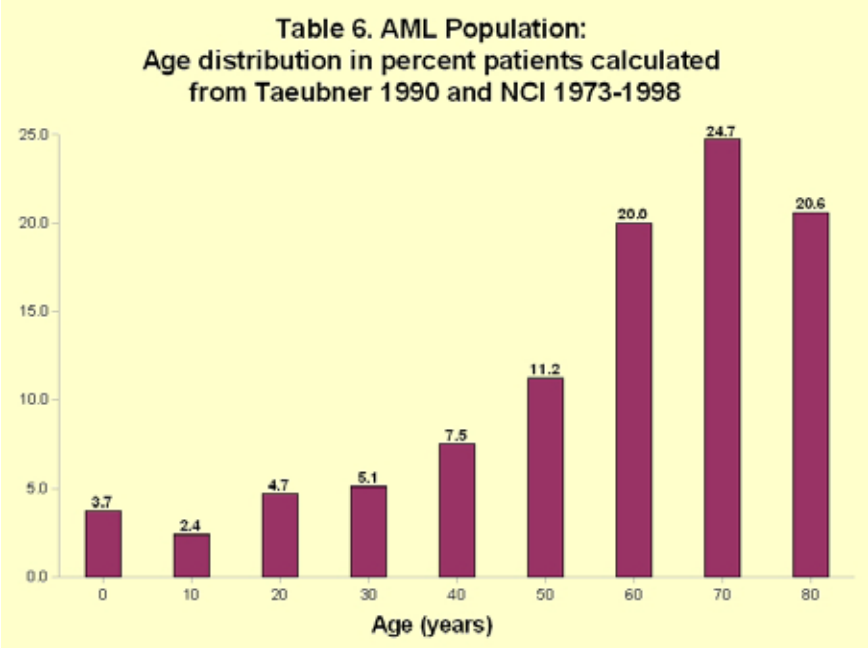
For continuous complete AML remissions at 4-5 years, the cure rate increases from 17% to 34% in younger patients, a double cure rate. In older patients there is an increase from 11% to 15% only. So, in comparison to the younger patients group, older patients do worse.

The German Acute Myeloid Leukemia Cooperative Group started its work in 1978. Our first observation was that patients who did not receive any post-remission chemotherapy have no chance of a longer relapse-free survival. In the following years we intensified our chemotherapy step-by-step by giving consolidation and maintenance. By double induction and maintenance, the cure rate of these patients was raised to 35%, which was, however, not enough. Yet the good point about this is that these are the results for patients of all age groups.

We tried to improve the results by further intensifying chemotherapy. By HAM-HAM induction, randomised against TAD-HAM, representing a difference in dosage of factor 2 there was no difference in the overall survival. And this lesson shows us that once a certain intensity of chemotherapy has been reached, we may not be able to further improve the results. Those may in fact be the limits of cytotoxic treatment. So we have to look for alternatives. This is true for patients of all ages.



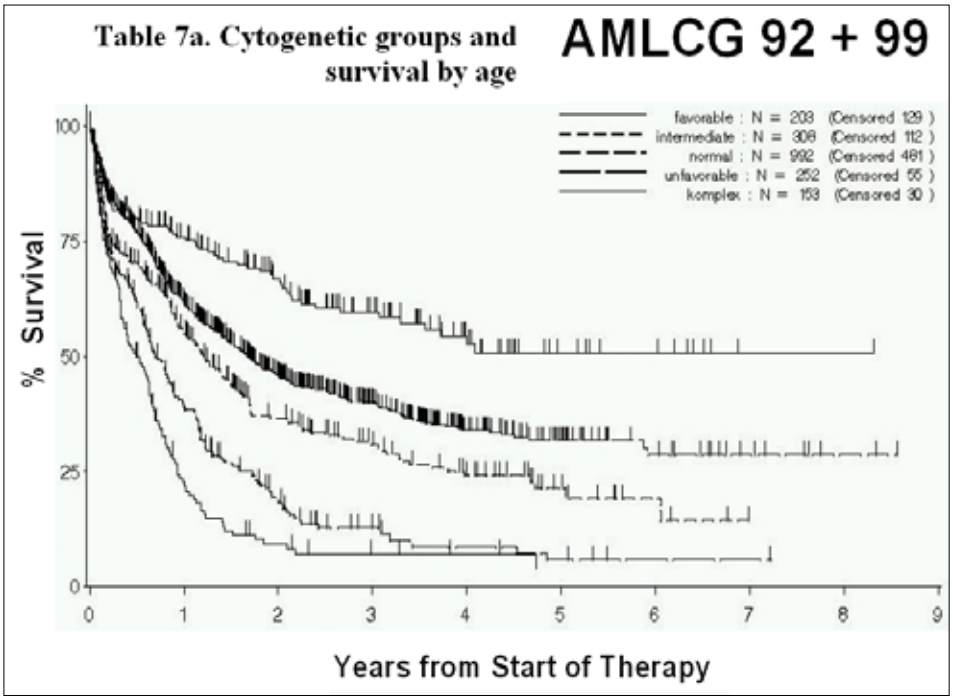
The overall survival of older patients amounts to only half of the overall survival of younger patients. So the situation for older patients is two times worse. This is a very important finding because two thirds of our patients are 60 years of age or older.

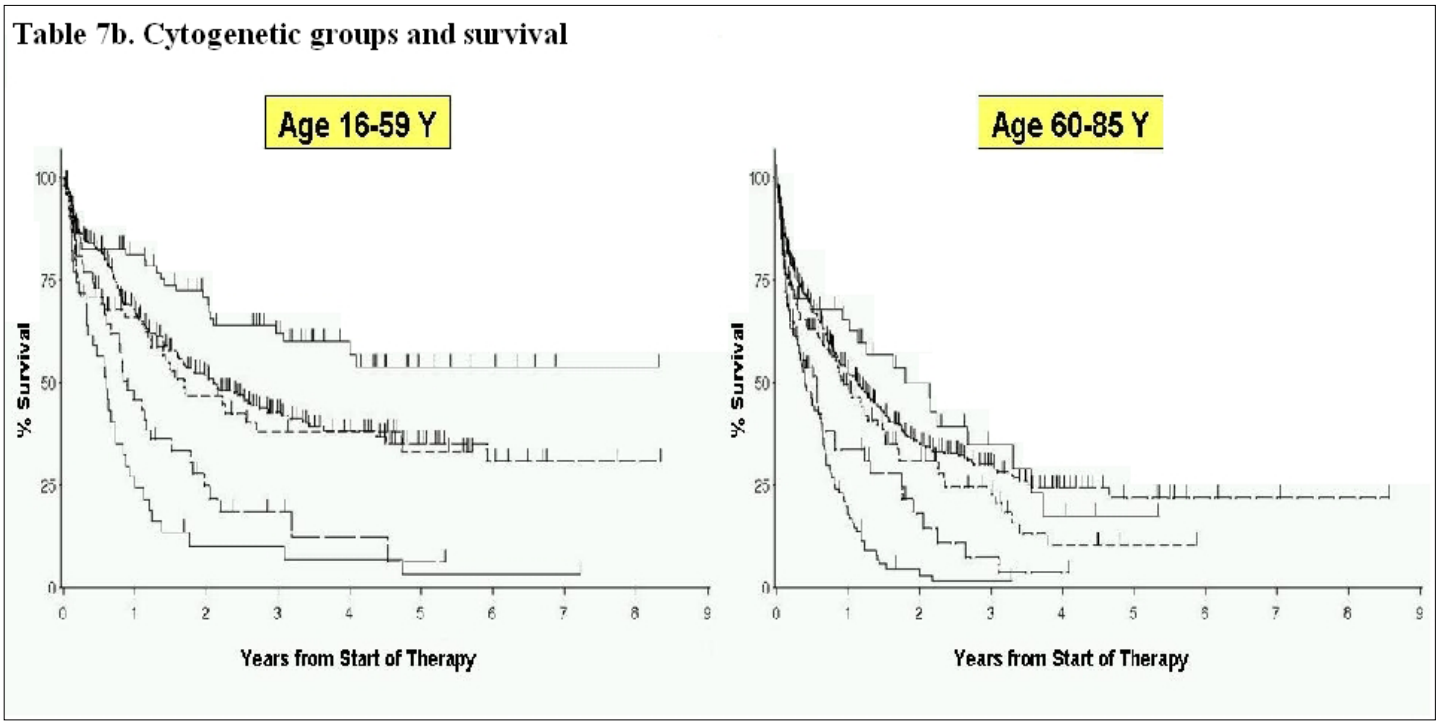


AML is a disease of older people. The treatment of older age AML is a challenge for the future. The challenge is to improve the results not only in the children, but also in the grandparents.

We also have to look at the chromosomes that show typical abnormalities in AML. These abnormalities give predictions for different outcomes in patients.

A favorable cytogenetic group is associated with a relatively long overall survival on the top and unfavorable cytogenetics predict for a short survival (on the bottom). And in between, three other groups of outcome in AML (AMLCG). So we can establish a hierarchy of classification on the basis of cytogenetics.





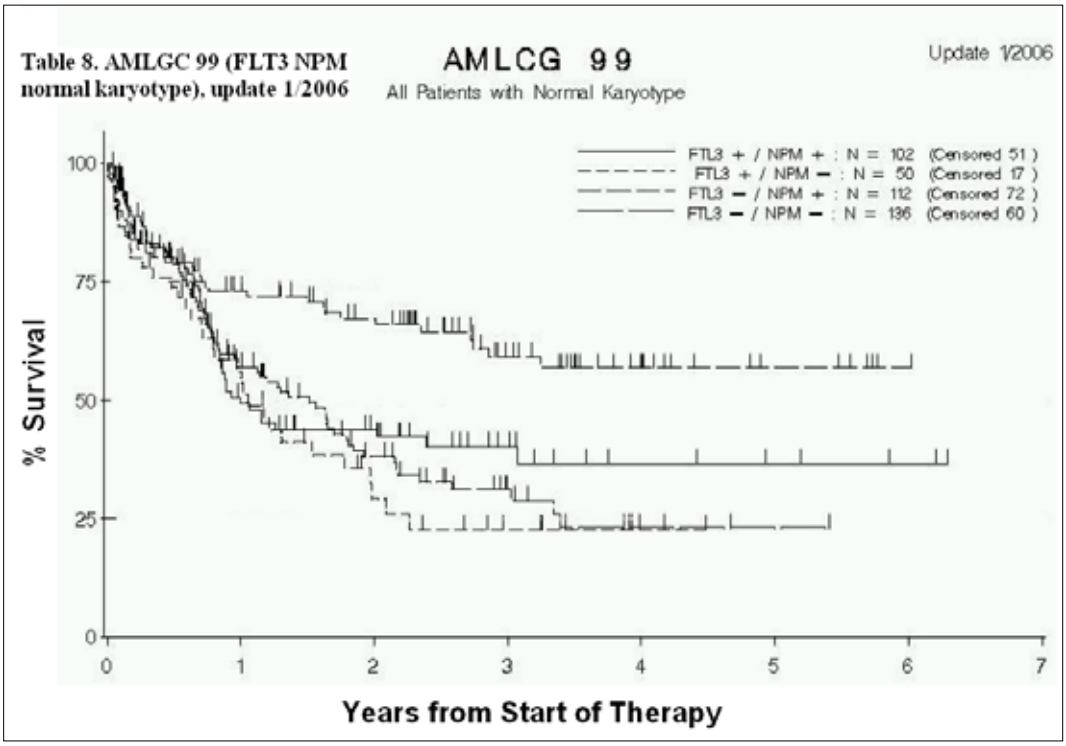
This slide shows that this classification is maintained in both age groups, in the younger patients on the left and also in the older patients on the right. But you see that in the older patients the general survival is significantly lower, which proves that the situation for older patients is worse.

We also have to look at the genes and their mutations as discovered more recently. We are in a position to find out particular genes and their mutations. This is especially important in the patients with normal karyotypes. Since half of the patients have normal karyotypes, we cannot classify them by cytogenetics.

In contrast to other combinations of the two genes, we need this again for classification. And we need the mutations in the future for therapeutic targets, of course.

There are some important mutations, such as mutations of the nucleophosmin1 gene in an acute myeloid leukemia (NPM), particularly when combined with the absence of an FLT3 mutation.

This combination really predicts a favorable outcome for patients of all ages.



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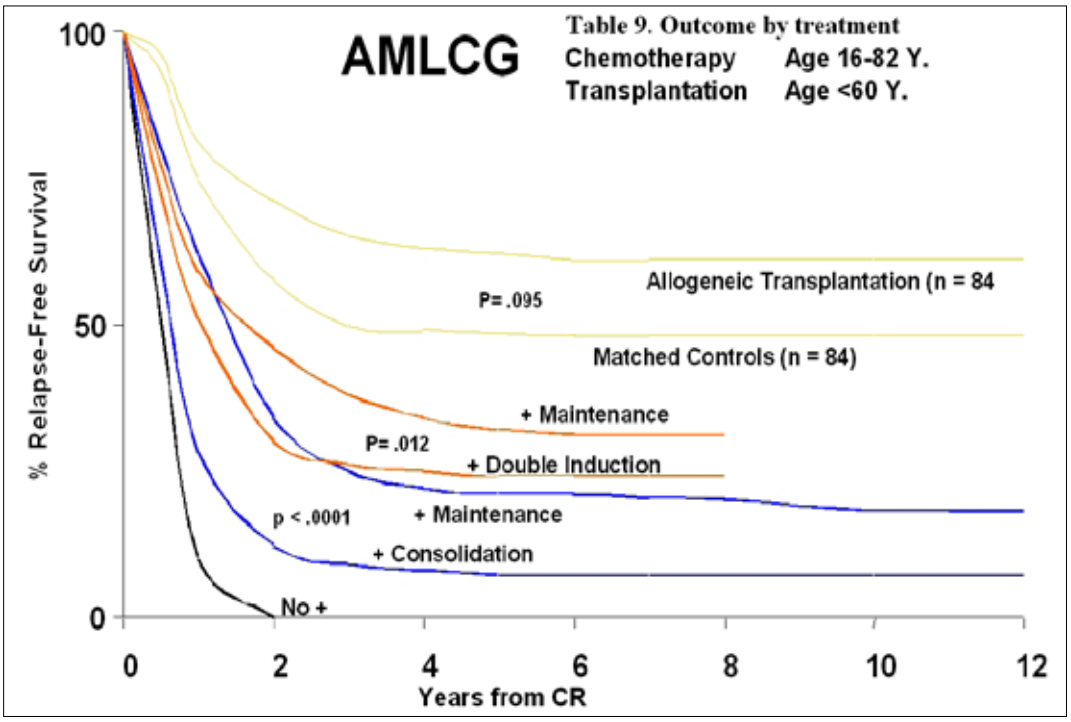
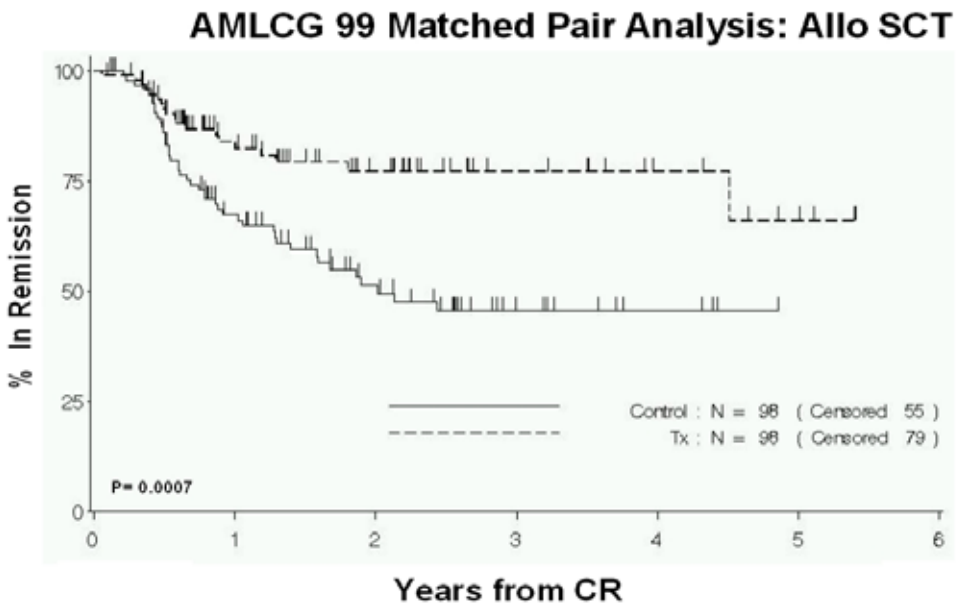


This slide shows the steps of improvement of chemotherapy together with allogeneic transplantation. Allogeneic transplantation represents the most important alternative to chemotherapy. Moreover, allogeneic transplantation appears

superior to chemotherapy. However, it is difficult to measure it. There are different approaches. One approach is Match Pair analysis. You see 84 transplantations compared to 84 chemotherapy patients in the Matched Pair system. And you see some superiorities which are not quite significant.

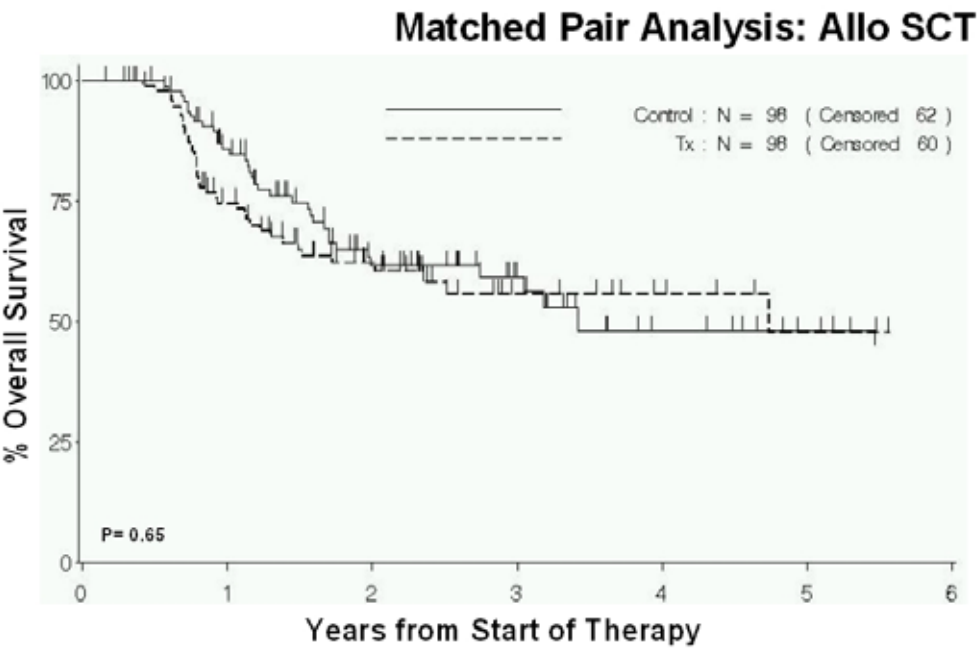
Furthermore, here, allogeneic transplantation appears highly superior to chemotherapy. However, you have to keep in mind that transplant patients are positively selected patients. In addition, they are younger than 60, in contrast to the chemotherapy patients, who are of all ages. However, allogeneic transplantation looks promising.

Table 10. Remission duration by treatment



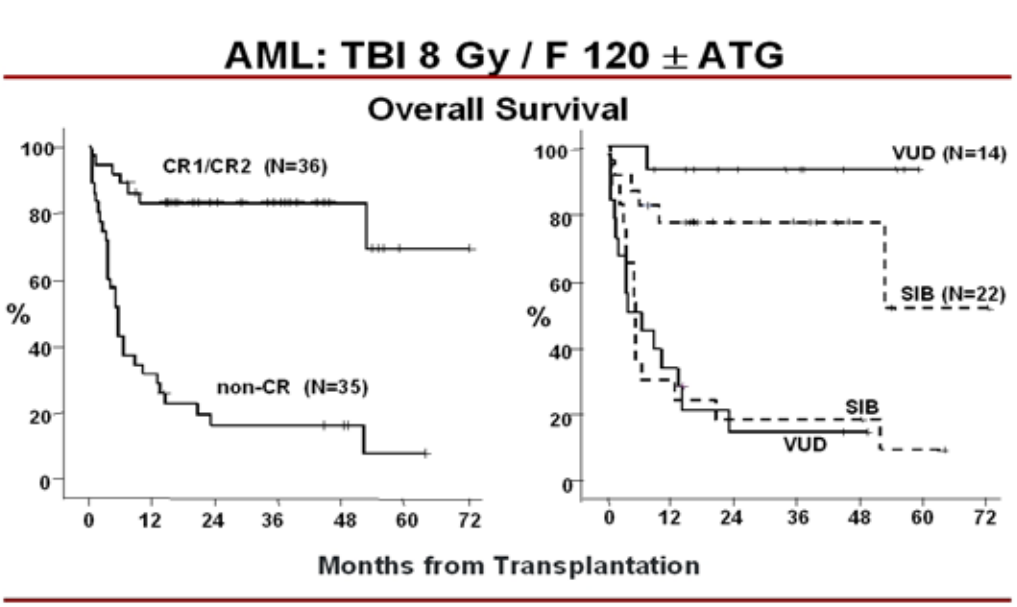
Here we did additional comparisons and analyses of allogeneic transplantation. The slide presents Matched Pair Analysis of 98 chemotherapy patients. A transplant is highly superior in the probability to remain without relapse. Those patients mostly do not relapse.

Table 11. Overall survival by treatment



However, if you look at the overall survival of these patients they become superimposable. This teaches us that allogeneic transplantation in all adults is associated with considerable mortality. We need to find out how transplant associated mortality can be overcome. This would really bring us much forward.

Graph 1. Overall survival



This could be done for instance by reduction in the Total Body Irradiation here at 8 Gy instead of 12 Gy. In this study it led to a high cure rate for the transplant patients, even in their overall survival. It looks like the transplant associated mortality was overcome in this study. And this is very encouraging. I heard from Hans-Jochem Kolb that this is also possible by reduction in chemotherapeutic conditioning of patients with similar results.

It is very promising also for our older patients. Patients even

Table 12.

over 60 years old and even over 70 years old may be treated by allogeneic transplantation in the future.
We also need better cooperation and we try to have it in the European Leukemia Network which is being funded by the European Commission in Brussels. In this network we combine a huge number of centres, of countries and of investigators.

We also created a network of multicenter therapeutic trials for AML. For such trials, researchers normally don't cooperate but rather compete with each other. But here they are cooperating using the instrument of a common standard arm.

The first symposium of the European Leukemia Network was in 2004. President Mikhail Gorbachev sent us a greeting address.

Table 13. Letter by Mikkhail Gorbachev to LeukemiaNet 2004

Heidelberg, January 2004

European LeukemiaNet

Dear Friends!

This symposium held at the German Cancer Research Center (DKFZ) in Heidelberg is an important landmark not only in the development of medical science in our continent but in the European life, too. Indeed, it has begun the new association's regular practical work whose purpose is to apply a joint effort and try to fight one of the gravest, dreadful and hard to cure diseases known in the 20th century and the just started 21st century. This association goes under the name "European LeukemiaNet".

"European LeukemiaNet" founders have set themselves an extremely challenging task, but they have every ground to expect success: they proceed from the premise that a closer cooperation, a faster exchange of information between physicians and scientists within "LeukemiaNet", can help them more accurately discover the disease's root causes, improve the patients' living conditions and raise the number of people cured of leukemia.

From the bottom of my heart I am greeting all those who have supported this noble initiative that gave new hope to many people. I shall try my best to contribute in this benign cause: at the request of the organizers of the network I agree to assume patronage over its work.

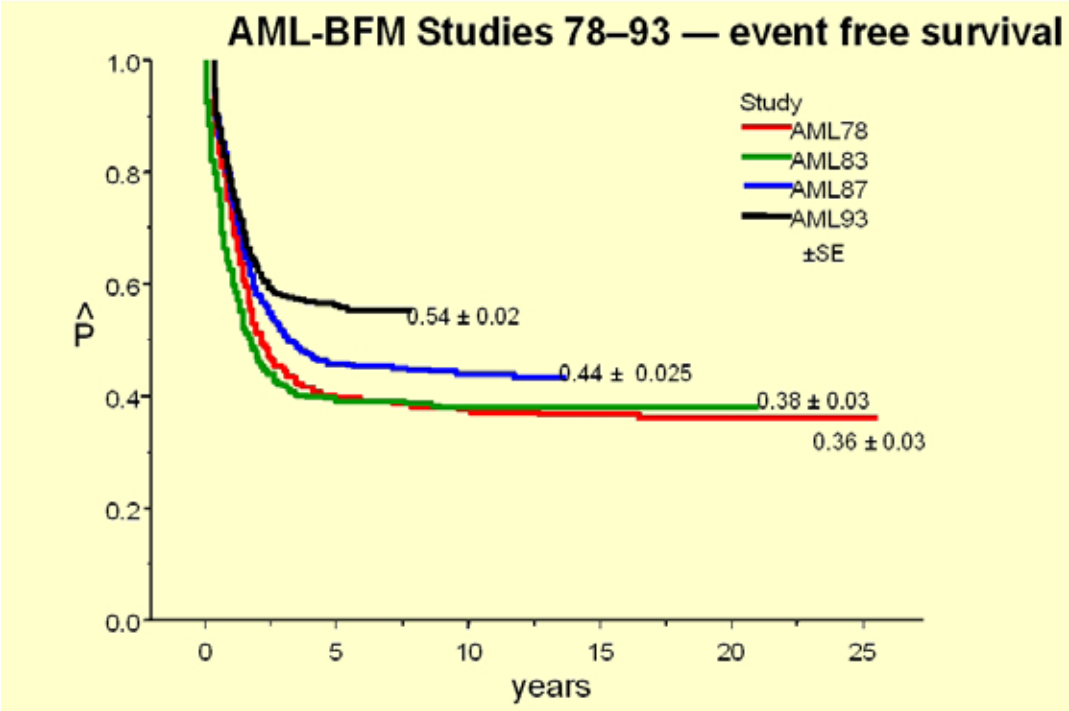
Respectfully yours,
Mikhail Gorbachev

The next annual meeting will be in January 2009. We are hoping for Mikhail Gorbachev to join us in this meeting and to speak to us.

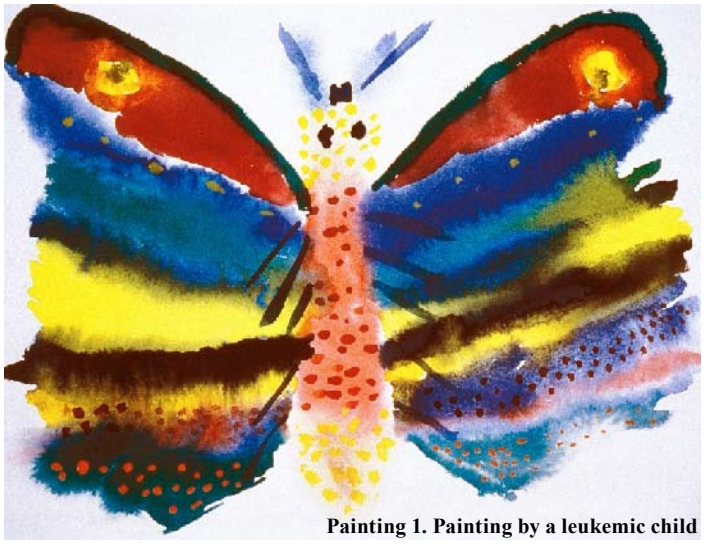
We like to learn from paediatricians.

My colleague, Professor Ritter, from our university, gave me the following slide about AML-multicenter-BFM trial, the Berlin/ Frankfurt/ Munich trial. And you see a stepwise improvement of the results according to the optimisation. A similar picture as in the adults.

Table 14. AML-multicenter-BFM trial, the Berlin/ Frankfurt/ Munich trial, slide by J. Ritter 2007



Paediatricians have a lot to teach us and we appreciate learning from them. More than 15 years ago, while in St. Petersburg with Boris Afanasyev, Edith and I met a family, with a little girl just undergoing allogeneic transplantation from her sister. She is now a medical student.



Painting 1. Painting by a leukemic child

Raisa Gorbacheva, 1999

Ladies and Gentlemen,

I hope I could give you a taste of the efforts required for helping patients with Acute Myeloid Leukemia, efforts of investigators, efforts of clinicians, and efforts of dedicated persons, their sponsorship, their organisation, their political work, let me say, their spirit.

And this is the contribution of Raisa Gorbacheva.

We will never forget Raisa Gorbacheva. We, our children, our grandchildren, and even history will not forget Raisa.

Thank you.

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