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Raisa Gorbacheva Memorial Lecture
Treatment of acute myeloid leukemia: Present status and new directions III

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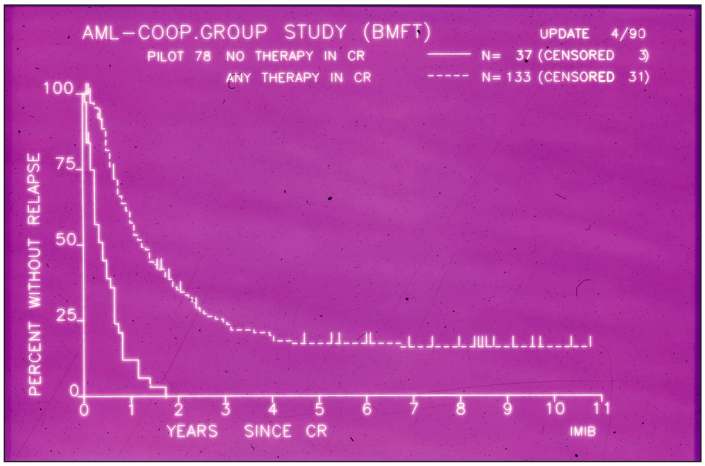
Since my 1st Raisa Gorbacheva Memorial Lecture 2 years ago things have changed in part whereas other things remain unchanged and appear more and more consistent.

Unchanged are the data from the numerous international multicenter trials published since 1981 covering both younger and older patients. The extract from these trials shows an increase of the mean complete remission rates between the 1980s and thereafter from 66% to 72% in younger and from 42 to 51% in older patients. Similarly, the rate of continuous complete remissions has increased over time from 17 to 34% in younger and 11 to 15% in older patients. During this period of time we also learnt about the effects of different treatment options. Thus, in our 1978 pilot study we made the observation that patients receiving any type of post-remission chemotherapy achieved some long-term remission rate, whereas patients not receiving post-remission chemotherapy all relapsed: mostly within the 1st year (fig.1) (1).

Patients receiving post-remission consolidation and were randomized to receive prolonged maintenance chemotherapy showed a significantly longer relapse-free survival than those randomized to no further treatment (1). A similar randomization between prolonged maintenance and high-dose AraC consolidation groups resulted again in a significantly superior relapse-free survival in the maintenance arm (2). In the current AMLCG trial patients were randomized upfront between double induction with standard dose and high-dose (TAD–HAM) chemotherapy versus two courses of high-dose chemotherapy (HAM–HAM). This big difference did not translate into a difference in the overall survival or in the relapse rate of either younger or older patients (3). The effect of autologous stem cell transplantation versus prolonged maintenance chemotherapy has also been investigated using upfront randomization. There was no difference in outcome neither by intention-to-treat nor by analysis as treated (3). In an attempt to possibly enhance the anti-leukemic potential of chemotherapy, patients assigned upfront randomization received G-CSF priming before and together with all chemotherapy courses during the first year. This modulation failed to change the outcome (4).

Figure 1. Remission duration in the 1978 pilot study by the AMLCG: the effect of no versus any post-remission therapy



A large-scale comparison between different treatment strategies became possible through a network of 4 multicenter randomized AML trials in Germany (AML Intergroup). The different trials were connected with each other by a common standard treatment arm containing 10% of patients from each trial recruited via a general upfront randomization (5). There were fundamental differences in the designs of the trials, which

used chemotherapy of differing intensity, and different assignment to treatment alternatives either via a randomization process or according to risk factors (fig.2), and also different preferences for allogeneic stem cell transplantation. Nevertheless, the long term overall survival in the 2784 patients under 60 years of age shows an almost identical 40–45% projected to 4 years (fig.3). A similar concordance is found in the relapse-free survival.

Figure 2. Study network of the German AML Intergroup: 4 independent and different AML trials are combined by the uniform standard arm and the general up-front randomization.

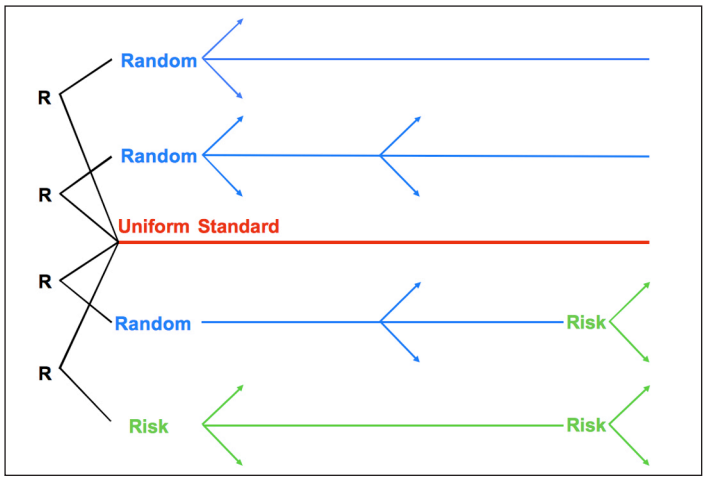
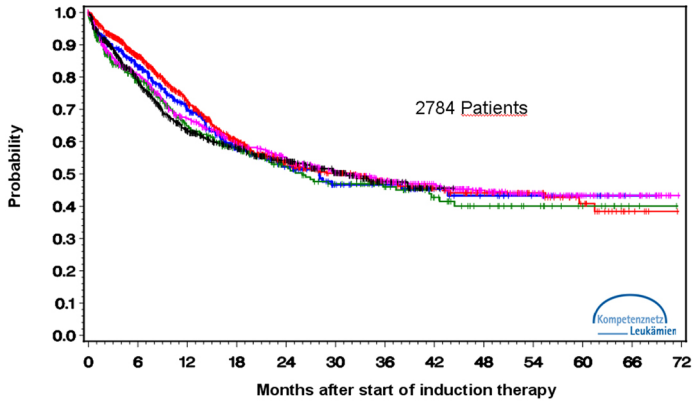


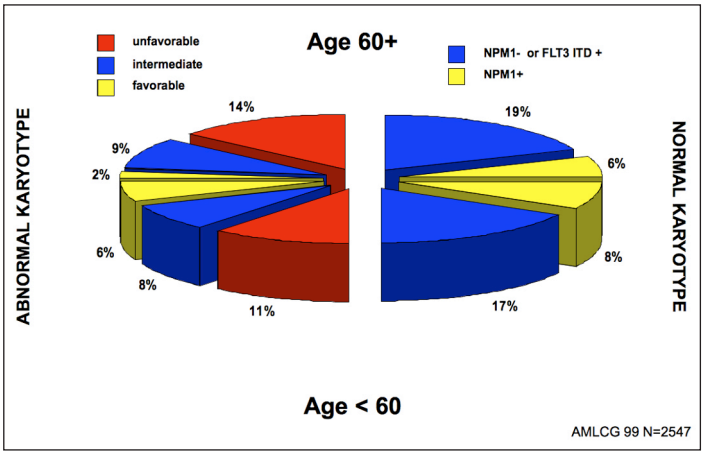
Figure 3. Overall survival in the 4 trials and the standard arm: Update from the AML Intergroup.



In a summary of the multiple international trials, the series of trials by the AML Cooperative Group, and finally the updates from the AML Intergroup, the anti-leukemic potential of chemotherapy as administered so far remains limited and may not be further improved by intensification. In contrast, the potential of chemotherapy appears to be exhausted.

The way forward might be more differentiated and distinctive. The direction is given by genetic classification of the individual AML. This is provided by the established chromosomal abnormalities that are found in only about half of the patients. More recently the other half exhibiting normal cytogenetics can be classified via gene mutations, the most prognostic of which are mutations of the NPM1 gene and internal tandem duplications of the FLT3 gene. Their combination allows identification of a rather favorable and a rather unfavorable prognostic group of patients (6). In the meantime many different mutations and their combinations have been described with marked influences on the outcome, such as the CEBPαgene mutation. The mutations and combinations other than NPM1/FLT3 contribute prognostic factors for only small groups of patients. The vast majority of AML patients can be prognostically classified on the basis of 3 factors: Age (younger versus older than 60 years), abnormal karyotype favorable versus intermediate versus unfavorable, and normal karyotype with isolated NPM1 mutation versus FLT3-ITD (fig.4).

Figure 4. AML risk groups defined by age, karyotype, and NPM1/FLT3 mutation status.



Now what about the role of allogeneic stem cell transplantation in AML? Allo SCT certainly represents a leading treatment option for AML. This becomes obvious when we look at the effect of allo SCT both from related and unrelated donors in patients carrying the most unfavorable genetic marker of a complex karyotype abnormality. And what about the general use of this option in the case of 1st complete remission? A large meta-analysis of European trials came to the result that patients younger than 35 with no favorable cytogenetics benefit from a superior relapse-free survival and even overall survival when analyzed on the basis of donor versus no-donor. Before we can accept this as a treatment of choice we should also ask for a similar donor versus no-donor analysis restricted to tissue-typed patients and siblings. This kind of analysis may be under way in the meantime. We must be aware

that comparative studies on the effect of allo SCT in 1st remission are difficult and subject to bias. As a useful compromise our group prefers to compare patients who underwent allo SCT with chemotherapy patients who are pairwise comparable in major risk factors such as cytogenetics, age, de-novo/secondary AML, type of induction treatment and follow-up time. Using this matched pair analysis in 135 transplanted patients we see a highly significant superior relapse-free survival, whereas the overall survival is not significantly different as an effect of the substantial non-relapse mortality in the transplant group. More recently the transplant-related mortality may be overcome through the use of a reduced intensity conditioning such as TBI 8 instead of 12Gy together with fludarabine and ATG, resulting in a high plateau even for the overall survival, equally in the transplants from siblings and unrelated donors when transplanted in 1st or 2nd complete remission (7). Gratwohl (8) has shown that in high numbers of European allo SCT patients the transplant-related mortality appears significantly decreased over time, also in AML. As mentioned before the benefit from allogeneic SCT may depend on the risk classification. As shown by the AMLSG, a benefit in the relapse-free survival seems to be restricted to patients with unfavorable gene mutations and not to be seen in patients with favorable mutations (9). Mutations may even provide an algorithm for prioritized treatments. This algorithm includes FLT3 and NPM1 mutations and hyper-expressions of the BAALC gene (10). We can also learn from the experiences of the pediatricians on risk-oriented allo SCT. I am grateful to my colleague Jörg Ritter for providing me with some data. The German BFM Group (Berlin, Frankfurt, Münster) restricted allo SCT to high-risk AML and available family donors. In their donor versus no-donor analysis there is some trend toward longer overall survival in the donor group, but this is not significant (11).

In summary of the conflicting data on allo SCT in AML we can conclude at the moment that there is good justification for allo SCT if a family donor is available, and that there is a clear indication for allo SCT even from an unrelated donor in adult high-risk AML. In an attempt to further define the role of allo SCT in AML we are about to start a strictly prospective multicenter trial where patients are randomized between allo SCT from related or unrelated donors in 1st remission versus after relapse. We strongly feel that this question can only be addressed in a randomized fashion.

Apart from allo SCT, novel targeted treatments will increasingly be integrated into the armamentarium against AML. Among a few examples, Rolf Mesters and his group (12) could demonstrate a complete response to a tyrosin kinase inhibitor with neutrophil and platelet recovery in a refractory AML. Alan Burnett and the MRC Group randomized their patients between chemotherapy alone or additional Gemtuzumab Ozogamicin (Mylotarg), and found a superior disease-free survival and reduced relapse rate in the Mylotarg group with no advantage so far in the overall survival. In the meantime there is a long list of targets and targeted agents (table 1). The most popular ones are All Trans Retinoic Acid and Arsenic Trioxide, which have been successfully applied in APL; some inhibitors of FLT3 like Sorafenib and Midostaurin are being currently investigated in randomized trials (13), and agents like decitabine and 5-Azacytidine are targeting the hypermethylation of histone in AML (14). The novel targeted agents are particularly indicated in older age AML per se representing an own risk factor across all AML subgroups (15). In another year we should know a little more about the novel approaches in AML using allo SCT and targeted treatment. We will follow with great interest the further developments at the Raisa Gorbacheva Memorial Institute here in St. Petersburg.

Table 1

Targets	Approach
GvL target	Allo SCT (MRD, MUD)
RARA	ATRA
PML	Arsenic trioxide
BCR/ABL, c-kit	Imatinib, Dasatinib, Nilotinib
FLT3 (wild type and mutated)	Sorafenib, Midostaurin
Tyrosin Kinase	SU5416
Farnesyl-Transferase	Tipifarnib
DNA synthesis	Clofarabine
Histone deacetylation (HDAC)	Valproic acid
Hypermethylation (DNMT)	5-azacytidine, Decitabine
CD33	GO (Mylotarg)

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