Treatment of acute myeloid leukemia (AML): Recent results and new directions

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Acute myeloid leukemia (AML) is a major indication for hematopoietic stem cell transplantation (HSCT). Here we describe more in general the present status and new directions in the therapy for AML.

Status of survival and cure rates

What is realistically the overall complete remission (CR) rate achieved by chemotherapy in usual modifications? This can be calculated from the combined results of the large multicenter randomized trials published since 1980. [1- 32]

There is only a modest progress in the CR rates when publications until 1990 [5 – 9,11,30] are compared with those after 1990 [1-4, 10,12-29, 31, 32] (Table 1).

Table- 1; AML Complete Remission Rate in 16 325 Patients (32 Publications)

Publication Period	1980 - 90	1991 - 2004
Total	63%	65%
Age < 60	69%	72%
Age 60 +	45%	50%

Beyond the CR rate, the rate of continuous complete remissions (CCR) at 4-5 years calculated for the number of patients who went into CR is relevant to estimate the definite cure rate. Unlike the CR rate, a therapeutic progress over time is seen in the CCR rate. However, it is almost restricted, to the younger age group (Table 2).

Table- 2; AML Continuous Complete Remissions at 4 - 5 Years (32 Publications)

Publication Period	1980- 90	1991– 2004
Total	**16%**	**27%**
Age < 60	**17%**	**32%**
Age 60 +	**11%**	**14%**

Role of chemotherapy intensity

The longterm outcome reflected by CCR or relapse-free survival (RFS) appears to depend on the intensity of chemotherapy both in terms of its dosage and its duration, exemplified by 3 sequential trials of the German AML Cooperative group (Figure 1).

No consolidation or maintenance in a non-randomized setting is not associated with long-term RFS.[7] Consolidation and maintenance (for 3 years) produces superior RFS compared to consolidation alone.[7] And the novel strategy of double induction [18] followed by consolidation and maintenance is superior to the same sequence with 1 additional course of intensive consolidation instead of maintenance.[19]
Notably, the maintenance effect is even seen in patients at high risk according to age 60+, unfavorable karyotype, LDH>700U, and delayed bone marrow blast clearance.[19] Thus, a poor prognosis can be improved by intensified chemotherapy. The maintenance effect is even seen in the high risk group of patients at older age. Actually patients 60 years of age or older contribute 2/3 to the entire AML population.[33] An improvement in the older age group would therefore favourably influence the overall results in AML.
Since further intensification in myelotoxic chemotherapy is limited, new perspectives lie in more specific, targeted therapies.

Acute Promyelocytic Leukemia

The best example for a target group gives Acute Promyelocytic Leukemia (APL), pathogenetically associated with the translocation t(15;17) involving the retinoic alpha receptor gene. As shown by all-transretinoic acid (ATRA) the APL blasts are brought to terminal differentiation, where the differentiated granulocytes can still contain multiple Auer rods as they are typi-

cal for the immature blasts in APL. Thus, ATRA induces a CR avoiding the stage of bone marrow aplasia. This observation and successful results were first contributed by a group in Shanghai.[34] ATRA then formed the basis for its effective combination with cytotoxic agents, mainly idarubicin as in the AIDA (ATRA/idarubicin) regimen by the Italian GIMEMA group[35] and similarly by the Spanish PETHEMA group.[36] Comparable with these experiences, the combination of ATRA with standard chemotherapy and even high-dose araC produced long-term CCR above 80%.[37]
The new competitor to ATRA, Arsenic-Trioxide (ATO) has again been introduced by the group in Shanghai who first used it in APL relapse where they induced high rates of 2nd CR.[38] The use of ATO in newly diagnosed APL was first investigated by the group in Teheran and proved equivalent to ATRA in the CR rate and duration.[39] Meanwhile, the Shanghai group started a randomized trial comparing ATO with ATRA and ATO+ATRA with the latter combination producing 100% CR and no relapse projected to 2 years in limited numbers of patients.[40]

Novel approaches in AML

In Non-APL AML molecularly targeted approaches are right at their beginning and positive outcomes are limited to single cases. Thus, a receptor-tyrosin-kinase-inhibitor targeting c-kit, VEGF and FLT3 induced a sustained remission in a patient with 2nd relapse refractory to other options.[41]
The immunologically targeted combination of Gemtuzumab/ Ozogamycin (GO) binds to cells with the AML specific CD33 antigen. Given as single agent, GO proved successful in patients with AML relapse[42] and patients over 65 years with untreated AML.[43]
Targeting multidrug resistance (MDR1) the addition of the MDR inhibitor PSC-833 to chemotherapy did not improve the outcome in patients over 60 years of age (44), while in younger patients of $\leq$ 45 years it appeared to improve the overall and relapse-free survival.[45]
In an attempt to enhance the effect of chemotherapy on leukemic cells growth factors were used in several trials mostly not successfully. Recently, the HOVON group demonstrated an improvement of relapse-free survival by G-CSF priming.[20] A similar trial by the German AML CG failed to reproduce this effect, so far.[46]

Allogeneic transplantation: new directions

Allogeneic hematopoetic stemcell transplantation (HSCT) can be considered to provide the most potent antileukemic principle through its graft-versus-leukemia (GvL) effect. Unbiased intent-to-treat comparisons of allogeneic HSCT with chemotherapy (figure 2) or autologous HSCT[47] actually show significant advantages of allogeneic HSCT in the remission duration whereas advantages in the overall survival failed significance.

This shows that allogeneic HSCT is compromised by considerable treatment related mortality (TRM). Attempts to overcome this crucial problem are done by reduced intensity conditioning regimens. Prospective studies using total body irradiation (TBI) are on the way to find the optimal dosage between the conventional 12 Gy and the minimum administered 2 Gy. Preliminary data demonstrating adequate donor-type chimerism and low TRM are promising even in high-risk and/or older patients (personal communication J. Kienast et al.).

Legends to the figures

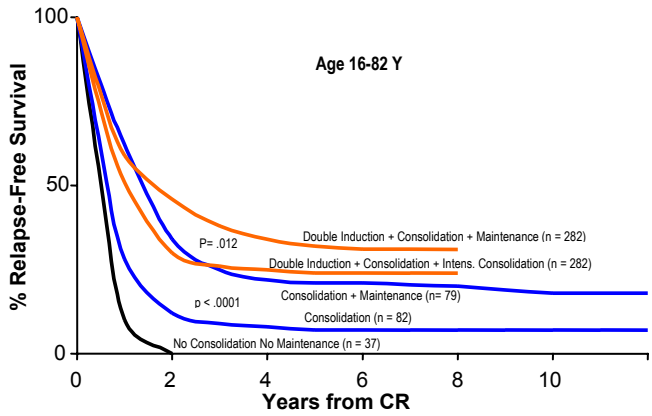
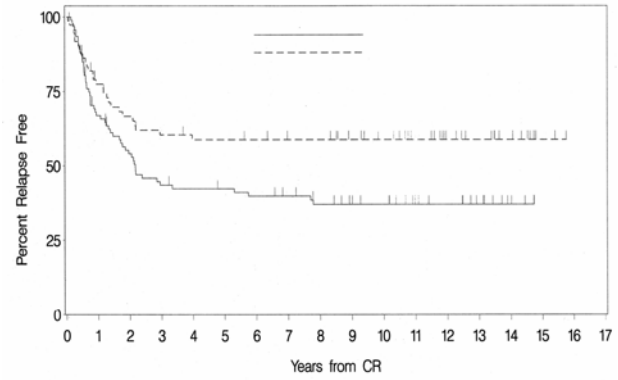


Figure- 1; AMLCG 78, 81, 86

Kaplan-Meier plots of relapse- free survival in adult AML patients at all ages, treated in 3 sequential trials by the German AML Cooperative Group. AMLCG 78, non-randomized trial, patients receiving no consolidation and no maintenance.[7] AMLCG 81, randomized trial, patients receiving either consolidation alone or consolidation + maintenance.[7] AMLCG 86,

randomized trial, patients receiving double induction, consolidation and either maintenance or intensive consolidation instead of maintenance (Figure 1).[8]



Intention-to-treat analysis of remission duration according to the presence or absence of a donor among siblings of patients with AML, included in the 1986 trial of the German AML Cooperative Group [Unpublished data] (Figure 2).

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