How I treat refractory and early relapsed acute myeloid leukemia

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Abstract

Between 10%-40% of newly diagnosed patients with acute myeloid leukemia (AML) do not achieve complete remission with intensive induction therapy and are therefore categorized as primary refractory or resistant. Few of these patients can be cured with conventional salvage therapy. They need to be evaluated regarding eligibility for allogeneic hematopoietic stem cell transplantation (HSCT) as this is currently the treatment with the highest probability of cure. To reduce the leukemia burden prior to transplantation, salvage chemotherapy regimens need to be employed. Whenever possible, refractory/relapsed patients should be enrolled in clinical trials as we do not have highly effective and standardized treatments for this situation. Novel therapies include tyrosine kinase inhibitors (TKIs), small molecule inhibitors (eg. for Polo-like kinase 1 (PLK-1), and aminopeptidase), inhibitors of mutated isocitrate dehydrogenase 1 (IDH1) and IDH2, antibody-based therapies and cell-based therapies. While the majority of these therapies are still under evaluation, they are likely to enter clinical practice rapidly as a bridge to transplant and/or in older, unfit patients who are not candidates for allogeneic HSCT. In this review we describe our approach to refractory/ early relapsed AML and we discuss treatment options for patients with regard to different clinical conditions and molecular profiles.
Introduction

Primary refractory acute myeloid leukemia (AML) and early relapse remain among the most challenging scenarios in the management of AML. Primary refractory or resistant disease as defined by not achieving complete remission (CR), i.e. a remaining blast count of 5% or more after one to two cycles of intense induction therapy,\(^1\) occurs in 10% - 40% dependent of the patient population. Early relapse (mostly referred to by relapse within 6 months after CR\(^1\))^2 must be differentiated from late relapse (>6 months) as response to salvage therapy and overall survival is significantly different.\(^3,4\) Treatment decisions must be carefully taken and alternatives weighted against each other by looking at the complex picture of the patient and his age, performance status, comorbidities, cytogenetic findings, molecular profile and patient preference.

The first question that we need to ask is whether there are means of reducing the risk for refractory disease and early relapse by the selection of the initial therapy, i.e. is there a superior induction therapy compared to standard “7+3” (7 days of cytarabine and 3 days of anthracycline)? While daunorubicin at 90mg/m\(^2\) certainly is superior to 45mg/m\(^2\) both in younger and the fit older patients\(^5,6\) including patients with \(FLT3-ITD\)^7, the direct comparison between daunorubicin 60mg/m\(^2\) with 90mg/m\(^2\) or 80mg/m\(^2\) did not demonstrate any difference as to CR rate and overall survival\(^8,9,10\) including patients with FLT3ITD\(^8\) although higher dose daunorubicin might improve outcome in core-binding factor AML.\(^11\) Thus, using 60-90mg/m\(^2\) daunorubicin or 12mg/m\(^2\) of idarubicin for three days is considered standard dosing. Whenever possible, we enroll newly diagnosed as well as relapsed patients into clinical trials.
Outside trials, we use ICE (idarabucin 12mg/m$^2$ days 1,3,5; cytarabine 100mg/m$^2$ continuously days 1-7; etoposide 100mg/m$^2$ days 1-3) as our standard induction therapy for fit patients tolerating intense treatment.\textsuperscript{12} In patients not fit for intensive chemotherapy, the induction therapy frequently has to be individualized taking patient and disease specific characteristics into account.\textsuperscript{13} Outside trials, decitabine is our first choice for elderly patients unsuitable for intensive therapy. In countries where decitabine is not approved yet, low-dose cytarabine may be used instead. By introducing you to two patients from our practice we would like to illustrate how we make treatment decisions for this patient group.

**Patient 1**

A 37-year-old woman was diagnosed with AML with 95% bone marrow blasts and a white count of 110,000/µL. Genetic analyses revealed a normal karyotype, a fms-like tyrosine kinase 3- internal tandem duplication ($\text{FLT3}$-ITD) with a length of 78 nucleotides and an allelic ratio of 0.67, and wildtype NPM1 and CEBPA. Induction chemotherapy with ICE was started but the patient still showed 60% of blast in the bone marrow on day 15 indicating poor response. Therapy with FLA-IDA (fludarabine, cytarabine, idarubicine)\textsuperscript{14} was immediately started as second induction cycle and in addition as a bridge to allogeneic HSCT. After this regimen the patient achieved a partial remission with 8% bone marrow blasts. After two weeks without further chemotherapy, conditioning with FLAMSA (fludarabine, amsacrine, cytarabine, 4 Gy total body irradiation (TBI))\textsuperscript{15} was initiated followed by allogeneic HSCT from her HLA-identical sister. Unfortunately, she relapsed 132 days after
allogeneic HSCT. In the relapse sample FLT3-ITD could be detected with an increase in the allelic ratio from 0.67 at time of diagnosis to 3.4 at time of relapse. After reduction of immunosuppressive therapy the patient was started on a regimen consisting of sorafenib and 5-azacytidine (AZA) based on phase-II data.\textsuperscript{16} With this regimen and two additional donor lymphocyte infusions the patient's AML was moderately controlled for two months. The aim was a second allogeneic HSCT with an alternative donor, but unfortunately she died due to septicemia related to her underlying AML.

**Discussion for Patient 1**

Before diagnosing primary refractory disease, one has to define the time point when this has been determined. Primary refractory disease is usually diagnosed in patients who have not achieved CR after two cycles after induction chemotherapy\textsuperscript{1}. Beyond this standard definition, it has consistently been shown that the prognosis is dismal in patients who are refractory to the first induction cycle as indicated by persistence of a substantial amount of bone marrow blasts at day 15 or who do not achieve at least a PR at day 21 to 35.\textsuperscript{17-19} Taking this into account, response-adapted induction therapy with dose intensification during the second induction cycle is frequently\textsuperscript{12,19,20} implemented in cases of insufficient response to first induction therapy as in our patient. In patient 1, the early assessment at day 15, which we routinely do in our practice, opened the possibility to intensify treatment in a timely manner. Based on our recent analysis intensification using either high-dose cytarabine in combination with gemtuzumab ozogamicin and all-trans retinoic acid or a regimen based on high-dose cytarabine plus fludarabine significantly improved the CR rate.\textsuperscript{21} The latter is in
line with the report from the MRC showing an earlier achievement of CR with FLAG-IDA compared to standard 7+3 induction therapy. Our patient responded rather well to FLA-Ida with 8% residual blasts and proceeded directly to an allogeneic HSCT. However, if the marrow had been hypoplastic with 5%-10% blast cells, we would have repeated the induction cycle with the identical chemotherapy as soon as clinically feasible, i.e. in the absence of uncontrolled infection, as these patients do as well with conventional chemotherapy as with high-dose cytarabine based regimens. Once these patients have achieved CR after the second induction cycle, they have the same long-term outcome as patients who achieve complete blast clearance with the first induction cycle. The question whether a second FLA-Ida before an allogeneic HSCT would have been beneficial cannot be answered based on currently available data. However, data from MRD assessment before allogeneic HSCT indicating that a lower leukemia burden with a negative MRD assessment before allogeneic HSCT is associated with a better outcome after transplant might be in favor of a second cycle. After early relapse, our patient received sorafenib, a multi-tyrosin-kinase inhibitor in relapse after allogeneic HSCT. The use of a sorafenib in this situation holds some promise, as sorafenib may synergize with allogeneic immune effects to induce remissions. Furthermore, there appears to be synergistic effects between sorafenib and azacitidine.

**Patient 2**

A 58-year-old female who was treated with standard intense therapy (ICE) in our institution for core-binding factor AML with inversion 16 (inv16) (cKIT wildtype) in an
interventional treatment trial. She achieved CR after one cycle of induction therapy but relapsed at 3 months after completing her consolidation therapy with three cycles of high-dose cytarabine. At the time of relapse the patient was pancytopenic with an ANC of 100/µl. An echocardiogram revealed a reduced cardiac ejection fraction (EF) of 44%. Based on high second CR-rates in patients with inv(16)-AML even in the situation of an early relapse we recommended an intensive salvage therapy in this situation. Because of her reduced EF the patient received a modified FLA-IDA regimen with liposomal daunorubicin replacing idarubicin. During therapy the patient became febrile and diagnostic work-up showed multiple nodules in a CT scanning consistent with aspergillosis of the lung. The patient was treated with antifungal therapy (voriconazole) but her respiratory situation did not improve and she needed mechanical ventilation. Granulocyte transfusions were given to the patient and she slowly improved and could be extubated. Her neutrophil count normalized on day 32. Bone marrow biopsy revealed a complete remission morphologically. The patient went on to allogeneic HSCT from a fully HLA-compatible unrelated donor using reduced intensity conditioning (RIC) according to the FLAMSA protocol. Three years later the patient is alive in CR.

Discussion for Patient 2

This patient showed two clinically relevant problems in the setting of her relapsed disease: cardiac insufficiency and uncontrolled infection. Cardiac insufficiency is especially relevant when anthracyclines are considered. Many patients with relapsed AML have already received high cumulative doses of anthracycline. In this situation,
replacing conventional anthracycline by liposomal daunorubicin should be considered as it does not reduce its efficacy\textsuperscript{27,28} while being less cardiotoxic as shown in pediatric AML protocols. Since prolonged neutropenia is a common problem in relapsed/refractory patients, fungal and bacterial infections present a major problem. For some patients not responding to broad-spectrum antibiotic or antifungal therapy granulocyte infusions can be helpful as a bridge to regeneration.\textsuperscript{29} Interestingly, patients with inv16 have a higher likelihood of responding to salvage therapy compared to patients in other cytogenetic groups including patients with t(8;21).\textsuperscript{30}

**If standard therapy fails**

Looking at the scenarios it becomes evident that there is not one standard therapy for all patients with refractory/early relapse AML. Is there a way to predict the probability of resistant disease at the time of AML diagnosis? Walter et al. tried to answer this question based on data from 4,601 newly diagnosed AML patients who were treated with standard induction therapy within the MRC/NCRI, HOVON/SAKK, SWOG or MD Anderson Cancer Center AML study groups. Prognostic factors for failure to achieve complete remission included age, performance status, white blood cell count, secondary disease, cytogenetic risk group and FLT3-ITD/nucleophosmin1 (NPM1) mutation status. However, the area under the receiver operator characteristic curves (ROC AUC) was only 0.78 meaning that it was difficult to forecast primary resistance based on these parameters.\textsuperscript{31} Nonetheless, there are clear associations of distinct genotypes and a high probability of resistant disease to induction therapy, e.g. AML characterized by a monosomal karyotype, an inv(3)/t(3;3) or a p53-alteration.\textsuperscript{32} Not only the likelihood of refractory/early relapse AML but also the
prognosis for refractory/early relapsed patients is dependent on cytogenetic and molecular features. Several scoring systems have been introduced for patients with refractory/relapsed AML in order to identify patients with an improved outcome including the one from the HOVON and the GOELAMS study group (Table 1).\textsuperscript{33,34} Cytogenetics other than favorable, mutated $\text{FLT3}$ ($\text{FLT3}$-ITD), higher age, previous HSCT and a short duration of first CR in relapsed patients were all adverse risk factors. Again our patients had different adverse risk factors. While patient 1 was young, her molecular profile revealed a FLT3-ITD as a risk factor. In patient 2, the inv16 was a favorable factor in the relapse situation. Similarly, relapsed patients with the genotype double mutated $\text{CEBPA}$ also have a high likelihood of a second CR and a favorable long term survival after allogeneic stem cell transplantation after relapse.\textsuperscript{35} When we diagnose primary refractory/early relapse AML, we decide primarily whether the patient is a candidate for allogeneic HSCT.\textsuperscript{12} At this point, allogeneic HSCT from a matched related or unrelated donor is the treatment strategy with the highest probability of cure,\textsuperscript{36,37} although survival does not exceed 20%-35% after 4 years.\textsuperscript{12,38} If not already done at the time of primary diagnosis, we initiate a rapid donor search. Risk factors prompting us to look for suitable donors already at the time of diagnosis include unfavourable cytogenetics based on ELN-recommendations\textsuperscript{2} and molecular markers including $\text{FLT3}$-ITD (especially if allelic ratios of $>$0.51).\textsuperscript{32,39,40} For us, there is no clear cut age limit for allogeneic HSCT. The hematopoietic cell transplantation (HCT)-specific comorbidity index introduced by Sorror et al in 2005 (and adjusted for age in 2014) gives a good guidance for comorbidity-associated risk assessment and should be calculated for all patients when considering transplantation.\textsuperscript{41,42}
If the patient is not a candidate for allogeneic HSCT (e.g. due to comorbidities or patient choice), we look at other treatment modalities including new drugs and/or palliative therapy with the aim to prolong patients` life with a meaningful quality of life (Figure 1). Outside trials, we start with low-dose cytarabine mainly to control leukocyte counts combined with best supportive care (blood transfusions, antibiotic/antifungal treatment). In some of our frailest patients, hydroxurea or 6-mercaptopurine to control hyperleukocytosis is currently the only treatment option. Palliative care services should be integrated in the patients` care. Calculations for the gain in quality-adjusted life-years (QALY) for different treatment options do not exist in Germany and are therefore not considered in our deliberations for treatment allocation.

**Chemotherapy before allogeneic HSCT**

If allogeneic HSCT is considered as best treatment option for the patient, we need to select the most promising salvage regimen to induce remission of the disease as a “bridge to transplantation”. The aim of the salvage therapy is to reduce the leukemic burden, as one of the most significant factors for all survival endpoints after allogeneic HSCT is the disease status before allogeneic HSCT. The lower the leukemia burden prior to transplantation the better the outcome. While salvage chemotherapy leads to CR rates of 40% to 60%, if CR duration was one year or longer, this rate drops to 10% to 15% in cases of shorter CR duration with the exception of AML- with inv(16) or double mutated CEBPA. Are there any superior salvage/second line chemotherapies? Salvage therapy often includes additional drugs that have not already been used during the first induction cycle. Although a
number of trials have examined different combination salvage therapies (Table 2),
there is still no commonly accepted standard in this situation. Whenever possible, we
include patients in a clinical trial for relapsed/refractory AML patients. Outside trials,
we use FLA-IDA as a salvage regimen.\textsuperscript{20,44-46} If there are no infectious complications
we do not add G-CSF to this regimen as there is no data supporting its use. However, idarubicin as an anthracycline appears to be an important drug in this
combination as FLA alone (fludarabine, high-dose cytosine) was inferior to ADE
(cytosine arabinoside, daunorubicin, and etoposide) as reinduction in a study for
relapsed/refractory patients.\textsuperscript{47} CR rates can be expected with this regimen in the
range of 30\% to 50\%.\textsuperscript{44} Other regimens are comparable in their effectiveness in this
situation. For instance, daunorubicin has been replaced by mitoxantrone as an
alternative anthracycline in combination with cytarabine and etoposide (MEC).\textsuperscript{48}
High-dose cytarabine in combination with mitoxantrone (HAM) is also a common
regimen in refractory/relapsed AML.\textsuperscript{49} Adding other purine analogs to salvage
chemotherapy is also practiced in this situation, but these drugs can increase toxicity.
The combination of clofarabine with high-dose cytarabine improved the response rate
compared to high dose cytarabine alone but not overall survival.\textsuperscript{50} Cladribine is also
an important purine analog used in the treatment of relapsed childhood AML\textsuperscript{51} while
not fulfilling its promise in relapsed adult AML.\textsuperscript{52} Sapacitabine is an oral purine
analog that was investigated in elderly AML patients with newly diagnosed AML or
relapsed AML showing some efficacy.\textsuperscript{53} When elacytarabine was compared to 7
other commonly used AML salvage therapies according to investigator’s choice,
outcome was not significantly different between patients receiving elacytarabine or
treatment in the control arm.\textsuperscript{54} Other modalities of reducing treatment toxicity is
liposomal delivery of chemotherapy. CPX-351, a liposomal formulation of cytarabine:daunorubicin, has shown good efficacy in treatment related AML. A recent phase II study evaluated CPX-351 versus intense salvage therapy in relapsed patients. Here, a benefit for CPX-351 was seen for relapsed patients with a poor-risk profile (see Table 1) with regard to response rates (39.3% vs 27.6%), event-free survival (EFS) and overall survival (OS).

**Donor selection for allogeneic HSCT**

Whenever possible, we aim for allogeneic transplantation for patients in second CR since there are essentially no cures with chemotherapy alone. However, if patients do not achieve a significant cytoreduction in the bone marrow or have more than 25% blasts in bone marrow, we usually abstain from transplantation and recommend hypomethylating agents or trial participation (and reevaluation after these therapies). The source of the graft (peripheral blood stem cells vs bone marrow) as well as matched related donor (MRD) or matched unrelated donor (MUD) do not impact significantly on outcome. If no HLA matched donor is available, alternative graft sources including cord blood or stem cells from a haploidentical donor should be considered in these high risk patients. However, in a head to head comparison results had been inferior with cord blood or haploidentical donors compared to MRD and MUD. For patients in second CR we tolerate less well matched donors since there are essentially no cures with chemotherapy alone in second CR.
Novel targets

It is unlikely that patients with refractory AML will be cured solely by changing and improving current chemotherapy regimens. The candidate targets for novel therapeutic approaches in AML are diverse (Figure 2). Some of these novel approaches have already been studied even in Phase III trials, others are just entering the early clinical trial phase or are under development. Although outside clinical trials the majority of these drugs are currently not available, we would still like to discuss these drugs because relapsed/refractory patients can be included in trials with these drugs and some of them are likely to be licensed soon. The list of targets and approaches is long and they can be classified in the following groups:

- Epigenetic modifiers (demethylating agents, histone deacetylase inhibitors)
- Antibody based therapies (eg. Gemtuzumab ozogamicin)
- Tyrosine kinase inhibitors (TKIs) (eg. TKI against FLT3-ITD)
- Small molecule inhibitors of kinases involved in cell division (eg. Polo-like kinase 1)
- Inhibitors of mutated enzymes (eg. inhibitors for IDH1, IDH2)
- Aminopeptidase inhibitors (eg. Tosedostat)
- DOT1L inhibitors (eg. EPZ-5676) for MLL-rearranged (MLL-r) leukemia
- Cell based therapies including chimeric antigen receptor therapy (CAR)
- Immunomodulating agents
The individual approach for each patient depends on several factors: patient’s molecular profile (eg. mutations in IDH1/IDH2, FLT3-ITD, MLL-r), trial availability, patient’s performance status etc.

Targeting FLT3

FLT3 is an important target for patients with an activating FLT3 mutation. While 30% of younger AML patients show a FLT3-ITD at the time of diagnosis, the percentage of patients rises in the population of patients with relapsed/refractory disease, as FLT3-ITD is highly associated with refractory/relapsed disease especially with a high allelic ratio. Several TKIs (eg. sorafenib, midostaurin, quizartinib, crenolanib) have been introduced to the treatment of these patients. It is important to keep in mind that these TKIs vary significantly in their specificity and their activity against resistance-conferring kinase domain (KD) mutations in FLT3. This may translate to differences in their clinical efficacy. Thus, it is unlikely that the question of the efficacy of TKIs will be solved in the very near future. FLT3 inhibitors as monotherapy have only led to transient responses. For some TKIs results from a phase 3 trial are available, while for others phase 1 and 2 trials are just being initiated. Should our 37-year old patient in case 1 have received targeted therapy with a TKI directed against FLT3 at the time of induction therapy or soon after? The answer is complex and cannot be definitely given at this point. In a randomized placebo controlled phase 3 trial no benefit was shown for elderly newly diagnosed AML patients treated with sorafenib in combination with intense therapy compared to patients receiving placebo. Importantly, there was also no outcome benefit seen in the very small subgroup of patients with FLT3-ITD treated with sorafenib, and patients in the sorafenib arm
showed a higher treatment-related mortality. However, a recently presented study in newly diagnosed younger AML patients showed a benefit for EFS and RFS if sorafenib was added to standard therapy. This effect was independent of FLT3 mutational status. Other TKIs against FLT3 include crenolanib, quizartinib (AC220), lestaurtinib, PLX 3397, ASP 2215 etc. They are currently being studied and hold promise due to the high selectivity for FLT3. Quizartinib has already been shown to be effective in patients with relapsed or refractory AML with FLT3-ITD and also some patients with wildtype FLT3. Lestaurtinib was evaluated against placebo in relapsed FLT3-ITD positive patients after receiving chemotherapy. Here, no benefit in survival or response was observed in the lestaurtinib treated patients. The expectations towards efficacy of a TKI against FLT3 might be scaled down by the fact that FLT3-ITD is likely not an early mutation in clonal evolution and thus less promising as a target.

Targeting IDH1/IDH2

Since the discovery of IDH1 and IDH2 mutations in ~10% of AML patients, inhibitors of IDH1 and IDH2 are already being introduced to clinical trials. Mutant IDH1 and IDH2 appear to be ideal pharmacological targets as enzymes can be more easily targeted compared to other mutated structures in AML. AG-221, an oral IDH2 inhibitor, is the first of its kind being already studied in a phase 1 dose escalation clinical trial. Here, AG-221 was studied as a monotherapy in IDH2 mutated patients and the clinical response rate was promising in the first interim analysis. The introduction of IDH1 inhibitors will follow.

Targeting MLL
A novel approach for AML with recurrent translocations at the 11q23 locus, referred to as MLL-rearranged (MLL-r) leukemia, is the DOT1L inhibitor EPZ-5676\textsuperscript{71} and palbociclib as a CDK6 inhibitor\textsuperscript{72}. Both are currently tested in clinical trials (NCT01684150, EudraCT2014-003647-34).

Targeting CD33

Gemtuzumab ozogamicin (GO) presents a combination of calicheamicin and a recombinant humanized IgG4 antibody directed against CD33. Several phase I/II trials have looked at its utility in primary refractory/relapsed disease but larger phase III trials in this setting are missing. CR rates between 32%-55% were observed for combinations of GO with chemotherapy.\textsuperscript{73-75} Interestingly, data from the MRC 15 trial showed that the addition of GO to induction therapy might be of significant benefit for patients with CBF AML.\textsuperscript{76} Although GO is not easily available outside clinical trials, we try to get this drug based on published evidence in elderly relapsed patients with CD33 expression of the blasts as a bridge to transplantation\textsuperscript{77}. GO has also been used in combination with demethylating agents such as vorinostat\textsuperscript{78} or azacitidine.\textsuperscript{79} These preliminary studies are especially promising for patients not tolerating intense chemotherapy, and modifications of the antibody and its linker might lead to further improvement. For patients who receive GO with the goal of allogeneic HSCT especially sinusoidal obstructive syndrome (SOS) of the liver is a concern.\textsuperscript{80} No clear risk factors for the occurrence of SOS during SCT could be identified, but the rate of death related to SOS was found to be small.\textsuperscript{80}
Other targets

The quinolone derivative vosaroxin inhibits the topoisomerase II and acts independently of the p53 mutational status. This drug was recently evaluated in combination with cytarabine (1g/m² on d1-5) in a phase 3 study in patients with refractory or relapsed AML. A benefit in overall survival of 1.4 months (7.5 months versus 6.1 months) was observed in the overall cohort that just missed significance. Inhibitors of cell division such as the polo-like kinase inhibitor (PLK-1) volasertib showed promise for AML patients. The oral aminopeptidase inhibitor tosedostat was studied in a multicenter phase II trial (NCT00780598) in elderly patients with refractory/relapsed AML with an overall response rate of 22%.

Immunologic approaches

Immune based approaches including chimeric antigen receptor therapies (CAR) are still very immature and the immense operating expenses do not allow a general approach at this point. However, already well known immunomodulating agents such as lenalidomide might play a role in future AML therapy, especially in low proliferative disease.

Finally, epigenetic modifiers could help patients with relapsed/refractory patients. Their role might be increased by combination therapy with novel agents (tosedostat, midostaurin) or as a bridge to allogeneic transplantation for less fit patients with the perspective of receiving RIC. This is based on the assumption that these drugs sensitize tumor cells to cytotoxic agents by re-expression of epigenetically silenced tumor suppressor genes.
In summary, the landscape of novel agents is very exciting and diverse. While some agents might only be applicable for molecularly defined subgroups of AML patients (eg. IDH1/2 mutations, FLT3-ITD, MLL-r), other agents hold promise for a broad unselected group of relapsed/refractory AML patients.

**Perspective**

The prognosis of refractory/early relapse AML patients remains poor even with allogeneic stem cell transplantation. Our insight into the molecular landscape of AML has dramatically increased with the introduction of next-generation sequencing as it has allowed us to identify novel genetic alterations including recurrent driver mutations. Functional analysis of these genetic aberrations has helped us to unravel the process of leukemogenesis further. For patients with refractory/early relapsed AML treatments arising out of these efforts present the most promising approaches.

**Author contributions:** F.T., R.F.S., M.H. and A.G. wrote the paper. All authors read and agreed to the final version of the manuscript.

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**Conflict of interest statement**

The authors have no potential conflicts of interest
References


8. Burnett A, Russell N, Hills RK, et al. A Randomised Comparison of Daunorubicin 90mg/m2 Vs 60mg/m2 in AML Induction: Results from the UK NCRI AML17 Trial in 1206 Patients *ASH Abstract.* 2014.


30. Schlenk RF, Benner A, Krauter J, et al. Individual patient data-based meta-analysis of patients aged 16 to 60 years with core binding factor acute myeloid


47. Milligan DW, Wheatley K, Littlewood T, Craig JI, Burnett AK, Group NHCO. Fludarabine and cytosine are less effective than standard ADE chemotherapy in high-risk acute myeloid leukemia, and addition of G-CSF and ATRA are not beneficial: results of the MRC AML-HR randomized trial. *Blood*. 2006;107(12):4614-4622.


67. Paschka P, Schlenk RF, Gaidzik VI, et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis...


81. Ravandi F, Ritchie E, Sayar H, et al. Improved Survival in Patients with First Relapsed or Refractory Acute Myeloid Leukemia (AML) Treated with Vosaroxin Plus
Cytarabine Versus Placebo Plus Cytarabine: Results of a Phase 3 Double-Blind Randomized Controlled Multinational Study (VALOR) ASH Abstract. 2014.


Table 1. Prognostic scoring systems for patients with refractory/relapsed AML.

<table>
<thead>
<tr>
<th>GOELAMS score&lt;sup&gt;34&lt;/sup&gt;</th>
</tr>
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<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>CR1 duration</td>
</tr>
<tr>
<td>≥ 12 months</td>
</tr>
<tr>
<td>≤ 12 months (refractory/early relapse)</td>
</tr>
<tr>
<td>FLT3-ITD status</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>positive</td>
</tr>
<tr>
<td>Cytogenetics§</td>
</tr>
<tr>
<td>Favourable/intermediate</td>
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<td>high risk</td>
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</table>

§ The cytogenetic risk group is defined according to MRC criteria<sup>85</sup>

Prognostic groups: good (0 points; OS 58%, event-free survival [EFS] 45% at 2 years); intermediate (1 point; OS 37%, EFS 31% at 2 years); poor (2-3 points; OS 12%, EFS 12% at 2 years)
**EPI score**

<table>
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<td>CR1 duration</td>
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<tr>
<td>≥ 18 months</td>
<td>0</td>
</tr>
<tr>
<td>7-18 months</td>
<td>3</td>
</tr>
<tr>
<td>≤ 6 months</td>
<td>5</td>
</tr>
<tr>
<td>Cytogenetics at diagnosis</td>
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<tr>
<td>t(16;16) or inv16</td>
<td>0</td>
</tr>
<tr>
<td>t(8;21)</td>
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<td>Other</td>
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<td>Age at relapse</td>
<td></td>
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<td>≤ 35 years</td>
<td>0</td>
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<td>36-45 years</td>
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<td>SCT before first relapse</td>
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C R, complete remission; SCT, Stem cell transplantation

Prognostic groups: favorable (1-6 points; OS of 70% at 1 year and 46% at 5 years), intermediate (7-9 points; OS of 49% at 1 year and 18% at 5 years), poor (10-14 points; OS of 16% at 1 year and 4% at 5 years)
Table 2. Trials with salvage regimens in refractory/relapsed acute myeloid leukemia.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Regimens</th>
<th>Number of patients</th>
<th>Refractory/relapsed</th>
<th>Median age (years)</th>
<th>% CR</th>
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<tbody>
<tr>
<td>Herzig et al, 1985*86</td>
<td>Phase II</td>
<td>HiDAC vs. HiDAC + DXR or DNR</td>
<td>78</td>
<td>42/36</td>
<td>37</td>
<td>63 vs. 65</td>
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<tr>
<td>Ho et al, 1988*87</td>
<td>Phase II</td>
<td>MTZ, etoposide</td>
<td>61</td>
<td>21/20</td>
<td>47</td>
<td>43</td>
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<tr>
<td>Amadori et al, 1991*88</td>
<td>Phase II</td>
<td>MTZ, etoposide, IDAC (MEC)</td>
<td>32</td>
<td>18/14</td>
<td>24</td>
<td>66</td>
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<td>Spadea et al, 1993*99</td>
<td>Phase II</td>
<td>MTZ, etoposide, IDAC (MEC)</td>
<td>74</td>
<td>0/30</td>
<td>37</td>
<td>55</td>
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<tr>
<td>Carella et al, 1993*90</td>
<td>Phase II</td>
<td>IDAC + Ida + etoposide</td>
<td>97</td>
<td>36/61</td>
<td>37</td>
<td>43</td>
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<tr>
<td>Ohno et al, 1994*91</td>
<td>Phase III, randomized</td>
<td>MTZ, etoposide, AraC + G-CSF vs. MTZ, etoposide, AraC</td>
<td>50</td>
<td>6/44</td>
<td>44 vs. 47</td>
<td>54 vs. 42</td>
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<td>Vogler et al, 1994*92</td>
<td>Phase III, randomized</td>
<td>HiDAC vs. HiDAC+ etoposide</td>
<td>131</td>
<td>n.g.</td>
<td>n.g.</td>
<td>31 vs. 38</td>
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<td>Archimbaud et al, 1995*48</td>
<td>Phase II</td>
<td>Etoposide, MTZ, AraC (EMA)</td>
<td>133</td>
<td>22/111</td>
<td>43</td>
<td>60</td>
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<td>Kern et al, 1998*93</td>
<td>Phase III, randomized</td>
<td>HiDAC + MTZ vs. IDAC + MTZ</td>
<td>186</td>
<td>27/159</td>
<td>50</td>
<td>47</td>
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<tr>
<td>Karanes et al, 1999*93</td>
<td>Phase III, randomized</td>
<td>HiDAC vs. HiDAC + MTZ</td>
<td>162</td>
<td>56/106</td>
<td>48 vs 53</td>
<td>32 vs 44</td>
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<tr>
<td>Thomas et al, 1999*94</td>
<td>Phase III, randomized</td>
<td>Etoposide, MTZ, AraC (EMA) + GM-CSF vs. EMA</td>
<td>192</td>
<td>120/72</td>
<td>47 vs. 46</td>
<td>65 vs. 59</td>
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<tr>
<td>Pastore et al, 2003*95</td>
<td>Phase II</td>
<td>FLAG-Ida</td>
<td>46</td>
<td>10/36</td>
<td>41</td>
<td>52</td>
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<tr>
<td>Wierzbowska et al, 2008*95</td>
<td>Phase II</td>
<td>Cladribine, HiDAC, MTZ</td>
<td>118</td>
<td>78/40</td>
<td>45</td>
<td>58</td>
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<td>Martin et al, 2009*96</td>
<td>Phase II</td>
<td>FLAG-Ida ± GO</td>
<td>71</td>
<td>10/61</td>
<td>48</td>
<td>29 (+GO) vs. 39 (-GO) (ORR 56 vs. 52)</td>
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<tr>
<td>Litzow et al, 2010*97</td>
<td>Phase II, randomized</td>
<td>IDAC + GO vs. IDAC + liposomal DNR vs. AraC, CTX, topotecan</td>
<td>82</td>
<td>29/53</td>
<td>60 vs. 52 vs. 53</td>
<td>12 vs. 7 vs. 4</td>
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<tr>
<td>Becker et al, 2011*98</td>
<td>Phase I/II</td>
<td>HiDAC + clofarabine + G-CSF</td>
<td>50</td>
<td>18/32</td>
<td>53</td>
<td>46 (ORR 61)</td>
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<td>Scappini et al, 2012*99</td>
<td>Phase II</td>
<td>IDAC + clofarabine</td>
<td>47</td>
<td>20/27</td>
<td>51</td>
<td>51</td>
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<tr>
<td>Jabbour et al, 2012*100</td>
<td>Phase II</td>
<td>BIDFA ± GO</td>
<td>93</td>
<td>n.g.</td>
<td>62</td>
<td>23 (ORR: 27)</td>
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<tr>
<td>Faderl et al, 2012*100</td>
<td>Phase III</td>
<td>IDAC + clofarabine vs.</td>
<td>326</td>
<td>171/148</td>
<td>67</td>
<td>35 vs. 18 (ORR: 31)</td>
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<td>Year</td>
<td>Chart</td>
<td>Trial Type</td>
<td>Treatment Description</td>
<td>CR (%)</td>
<td>Response Rate</td>
<td>Refs</td>
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<td>------------</td>
<td>---------------------------------------------------------------------------------------</td>
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<td>2012</td>
<td></td>
<td>Phase II</td>
<td>Homoharringtonine, AraC, aclorubicine</td>
<td>46</td>
<td>11/35</td>
<td>37</td>
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<td>Phase III, randomized</td>
<td>SHAI vs. SHAI + fludarabineIDAC + GO vs. IDAC + liposomal DNR vs. AraC, CTX, topotecan</td>
<td>326</td>
<td>n.g.</td>
<td>57 vs. 52</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(ORR: 42 vs. 54)</td>
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<tr>
<td>2014</td>
<td></td>
<td>Phase II, randomized</td>
<td>Fludarabine,HiDAC, liposomal DNRMTZ, etoposide</td>
<td>41</td>
<td>11/30</td>
<td>60</td>
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<td>2014</td>
<td></td>
<td>Phase III, randomized</td>
<td>Elacytarabine vs. others</td>
<td>381</td>
<td>140/241</td>
<td>59 vs. 60</td>
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<td></td>
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<td>(ORR: 23 vs. 21)</td>
<td></td>
<td></td>
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<tr>
<td>2015</td>
<td></td>
<td>Phase II</td>
<td>CPX-351 vs. first salvage therapy</td>
<td>125</td>
<td>125</td>
<td>52 vs. 56</td>
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</table>

Abbreviations: HiDAC, High-dose cytarabine; DXR, doxorubicin; DNR, daunorubicin; MTZ, mitoxantron; IDAC, intermediate-dose cytarabine; G-CSF, granulocyte-colony stimulating factor; FLAG-Ida, fludarabine + high-dose cytarabine + idarubicin + G-CSF; GO, Gemtuzumab ozagamicin; BIDFA, twice-daily fludarabine and cytarabine; SHAI, sequential high-dose cytarabine + idarubicin; CTX, cyclophosphamide; MEC, mitoxantrone + cytarabine + etoposide; AraC, cytarabine; CR, complete remission; REF, refractory; REL, relapsed; ORR, overall response rate
Figure 1. Algorithm for patients with early relapsed/refractory AML.

When diagnosing primary refractory AML/early relapse patients need to be evaluated for allogeneic hematopoietic stem cell transplantation and/or a suitable trial.

Abbreviations: HCT-CI, Hematopoietic Cell Transplant-Co-morbidity Index; FLA-IDA, fludarabine, cytarabine, idarubicine; MEC, mitoxantrone, etoposide, cytarabine; DLI, donor lymphocyte infusion; LDAC, low-dose cytarabine; TKI, tyrosine kinase inhibitors; FLT3-ITD, fms-like tyrosine kinase 3- internal tandem duplication; clinical trials should consider the patient’s performance status ie. Fit patients should receive more intense study medications (in most cases including chemotherapy) compared to unfit patients.

Figure 2. The candidate targets in AML.

Abbreviations: CD; cluster of differentiation; FLT3, fms-like tyrosine kinase 3; cKIT, tyrosine-protein kinase Kit; ras, rat sarcoma; IDH, isocitrate dehydrogenase
Figure 1

Refractory/Relapsed AML

Evaluation:
- Performance status (incl. HCT-CI score)
- Cytogenetics
- Molecular analysis

FIT (Go Go)
- Salvage therapy eg. FLA-IDA, MEC
  - Allogeneic stem cell transplantation
  - Tentatively eg. DLI, targeted therapy

Unfit (Slow Go/No Go)
- Clinical trial for fit patients#
  - Clinical trial for unfit patients$^
    - LDAC
    - Demethylating agents
    - Hydroxyurea
    - TKI (for FLT3-ITD)

- LDAC
- Demethylating agents
- Hydroxyurea
- TKI (for FLT3-ITD)
Figure 2

- Chimeric antigen Receptor (CAR)
- Tyrosin Kinase inhibitors (FLT3, cKIT)
- Aminopeptidase inhibitors
- Polo-like kinase1 inhibitors
- Demethylating agents
- CD
- CD33
- Gemtuzumab ozogamicin
- Farnesyltransferase inhibitors
- IDH1 inhibitors
- IDH2 inhibitors
- DNA
How I treat refractory and early relapsed acute myeloid leukemia

Felicitas Thol, Richard F. Schlenk, Michael Heuser and Arnold Ganser

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