12 Treatment of Refractory and Relapsed Acute Promyelocytic Leukemia

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Abbreviations

AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
Ara-C	Cytosine arabinoside
ATO	Arsenic trioxide
ATRA	All-trans retinoic acid
CIR	Cumulative incidence of relapse
CNS	Central nervous system
CR	Complete remission
EBMT	European Society for Blood and Marrow Transplantation
GVHD	Graft versus host disease
HSCT	Hematopoietic stem cell transplantation
NCCN	National Comprehensive Cancer Network
OS	Overall survival
PML	Promyelocytic leukemia
RARA	Retinoic acid receptor alpha
RT-PCR	Reverse transcriptase polymerase chain reaction
TRM	Transplant related mortality
WBC	White blood cell

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Introduction

The prognosis of patients with acute promyelocytic leukemia (APL) has significantly improved over the past decades. At least 80% of adult patients included in clinical trials can be cured. The first important step in the successful development of APL therapy was the availability of anthracyclines, the first drugs with a curative potential in APL [1]. The outcome was further improved by the introduction of the differentiating agent *all-trans*-retinoic acid (ATRA) and more recently by arsenic trioxide (ATO) [2]. Major challenges are the unresolved problem of early death and the optimal management of relapsed patients.

Although the recent use of ATO in frontline therapy was associated with an extremely low relapse rate [3, 4], the optimal management of relapse after ATO is not well defined. Current literature is mainly restricted to patients in first relapse after ATRA plus chemotherapy, and ATO-based salvage therapy enables cure in a considerable proportion of these patients. Further, current data suggest that long-term stabilization and cure may be possible even after subsequent relapses. This chapter focuses on current problems, treatment options, and outcome of patients with relapsed APL.

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Molecular Monitoring for Early Detection of Relapse

The induction and persistence of a molecular remission (negative RT-PCR for *PML/RARA*) are the prerequisites for long-term remission and cure in APL. Molecular relapse is conventionally defined as recurrence of a positive reverse transcriptase (RT) PCR or real-time quantitative PCR confirmed in two tests of bone marrow samples taken 2–4 weeks apart. As shown by follow-up studies, patients with molecular relapse usually developed an overt hematological relapse after a median time of 3 months [5]. Therefore, PCR monitoring offers the possibility to detect the relapse earlier on the molecular level and to avoid the problems and risks of an overt hematological relapse.

The benefit of molecular monitoring and of early intervention at the time of molecular relapse was shown in two retrospective studies comparing patients with APL in molecular and hematological relapse [6, 7]. Treatment at the time of molecular relapse was associated with a lower rate of complications during therapy such as early death and APL differentiation syndrome with a positive impact on survival. In a prospective British study for newly diagnosed APL patients, preemptive therapy with ATO for patients with molecular relapse was integrated in the study design. The cumulative incidence of overt hematological relapse (CIR) at 3 years was only 5% (on the UK-MRC AML 15) as compared to 12% in a previous British APL (AML 12) study [8]. The results argue in favor of regular molecular monitoring in first remission at least in high-risk patients treated with conventional ATRA and chemotherapy.

Given the high rate of stable remission after ATO frontline therapy, the value of molecular follow-up in this setting is questioned; thus molecular monitoring and its duration have to be determined individually.

Results with Conventional Treatment Strategies in Relapsed APL

The primary objective of relapse therapy in APL is the re-induction of molecular remission. With conventional approaches based on ATRA and intensive chemotherapy, remission rates of around 90% can be achieved, similar to frontline therapy [9–11]. But in the setting of salvage therapy, ATRA plus chemotherapy is no longer curative, and cure is only possible with subsequent allogeneic or autologous hematopoietic stem cell transplantation (HSCT) [12]. Especially for allogeneic HSCT, this approach may be problematic due to the reduced feasibility and failure rate of transplantation due to the high toxicity of intensified chemotherapy associated with neutropenia and infections. This was represented by the results of a French study including 50 patients with relapsed APL treated with ATRA, mitoxantrone, etoposide, and higher doses of Ara-C. Of 11 patients who underwent allogeneic transplantation, the 3-year survival rate was only 11% and the median survival 8.2 months. Causes of death in remission were infections or GVHD. Among 34 patients who were scheduled to receive an autologous HSCT, only 22 patients could be transplanted [11]. This demonstrates the need for less toxic salvage therapies for relapsed APL.

Current Approaches with ATO-Based Salvage Therapy

ATO-Based Induction and Consolidation Therapy

In the 1990s, authors from China reported the first clinical results on the successful outcome of patients with relapsed APL treated with ATO. Prominent results were the ability of the drug to induce long-lasting second molecular remissions and the low toxicity profile [13]. Subsequently, the high efficacy of ATO in relapsed APL was confirmed by phase II studies (reviewed in [14]). The drug was approved in the United States and in Europe for relapsed APL based on the results of the US Intergroup pivotal study, the largest trial including 40 patients in first relapse of APL. In this study, patients reached a complete remission (CR) rate of 85% and an estimated overall survival of 66% at 18 months [15]. A literature review summarized the results of more than 300 patients with relapsed APL treated with ATO between 1997 and 2011.

Approximately 40% of patients were already in second or more advanced relapse. The patients uniformly received ATO induction therapy (mostly 0.15 mg/kg/day). Post-induction treatment comprised up to five ATO courses and was often combined with chemotherapy. In, total, 59 patients proceeded to autologous or allogeneic HSCT. The average hematological CR rate was 86%, while early death and resistance rates were both at 7%. The rate of molecular CR reached 86% in the largest study with consequent molecular monitoring. The overall survival probability at 2 years ranged between 50 and 81% [14].

The clinical efficacy of the combination of the two differentiating drugs ATO plus ATRA was investigated in newly diagnosed and relapsed APL. The advantage of this combination was demonstrated by a faster and more extensive reduction of the *PML/RARA* burden and by a lower relapse rate [16]. A benefit of the combination was further suggested by the results of a meta-analysis of seven studies. These data showed that the combination of ATRA and ATO induced higher rates of CR and overall survival compared to ATO or ATRA alone without increasing early mortality or toxicity [17].

A registry study from the European LeukemiaNet included 155 patients with APL treated with ATO-based salvage therapy in first relapse after state-of-the-art frontline therapy with ATRA and chemotherapy (104 patients with hematological, 40 with molecular, 11 with extramedullary, mainly central nervous system (CNS) relapse) [18]. Salvage therapy was uniformly performed with one induction cycle ATO ± ATRA, followed by at least one identical consolidation course. Post-consolidation therapy consisted of autologous (n = 60) or allogeneic (n = 33) HSCT or of further ATO or chemotherapy (n = 55). After a median follow-up of 3.2 years, 3-year overall survival (OS) and cumulative incidence of relapse (CIR) of the whole population were 70% and 44%, respectively (Fig. 12.1a, b). This suggests a survival improvement of approximately 20% compared to previous results with ATRA and chemotherapy [10]. Patients treated for molecular relapse had decreased early death rate and better tolerance of the therapy (significantly lower rates of APL differentiation syndrome and of infections) in comparison to patients treated for hematological relapse. However, the survival advantage of patients with molecular relapse disappeared with longer follow-up (Fig. 12.2a, b). The multivariable analysis of prognostic factors for overall and leukemia-free survival demonstrated a positive impact of CR1 duration ≥1.5 years and achievement of a second molecular remission and of transplantation in second CR (allogeneic or autologous) [18].

Options for Post-consolidation Therapy

There is evidence from the literature that post-consolidation therapy with autologous or allogeneic HSCT or with prolonged ATO plus ATRA improves the outcome as compared to no further therapy [14]. In lack of randomized studies, the presently available guidelines (Europe, USA, Canada) are based on consensus recommendations.

In 2009, a panel of European APL experts published recommendations for the management of relapses on the basis of the available literature. The European recommendations indicate two cycles of ATO ± ATRA for induction and consolidation therapy followed by autologous HSCT, if a molecular remission was achieved after consolidation. For patients who fail to obtain a second molecular remission or who relapse after short CR1 duration of less than 1–1.5 years, allogeneic HSCT should be favored. For patients who do not qualify for transplantation, prolonged ATO plus ATRA therapy or chemotherapy intensification is recommended (Fig. 12.3) [19]. For the latter group of patients, the Canadian guidelines provided detailed information and recommended a sequence of six cycles of ATO plus ATRA [20]. The NCCN guidelines 2016 for APL relapse recommend an ATO-containing regimen for patients not previously exposed to ATO and for patients with later relapse (≥6 months) after previous ATO therapy. In patients with early relapse (<6 months) after an ATO/anthracycline containing regimen, standard ATRA plus idarubicin with the addition of ATO is recommended [21].

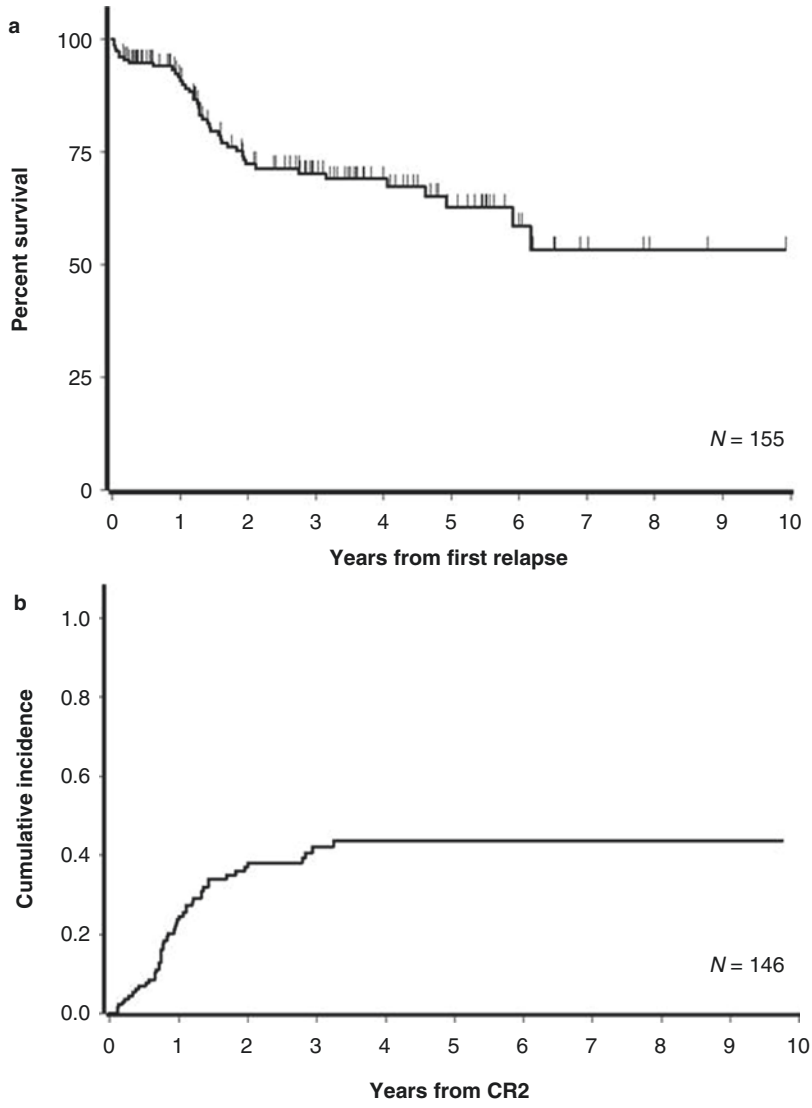

Fig. 12.1 Overall survival (**a**) and cumulative incidence of relapse (**b**) of all patients treated with ATO in first relapse of APL. Tics indicate the last follow-up of the living patients [18]

There are no randomized studies comparing autologous and allogeneic transplantation. Most data are available from retrospective comparisons. In general, autologous transplantation was associated with higher relapse probability but lower toxicity compared to allogeneic transplantation. The results of 122 relapsing patients included in the French/European APL91 and 93 trials showed a 7-year relapse-free survival rate of 79.4%, event-free survival of 60.6%, overall survival of 59.8%, and transplant-related mortality (TRM) of 6% in the autologous group. The respective results of the allogeneic group were 92.3%, 52.2%, and 51.8% and a TRM of 39% [22]. Similar data were reported from the EBMT registry and other smaller series [23]. A prospective Japanese study of 35 patients in first relapse treated with ATO and subsequent autologous transplantation showed a 5-year event-free and overall survival of 65% and 77%, respectively [24]. In a retrospective study of 31 Italian patients, who underwent allogeneic transplantation in CR2 or beyond, 4-year OS was 45%. Favorable prognostic factors for OS and CIR were molecular remission at transplantation and a lower number of relapses [25].

Other retrospective studies compared the outcome of transplantation, almost always

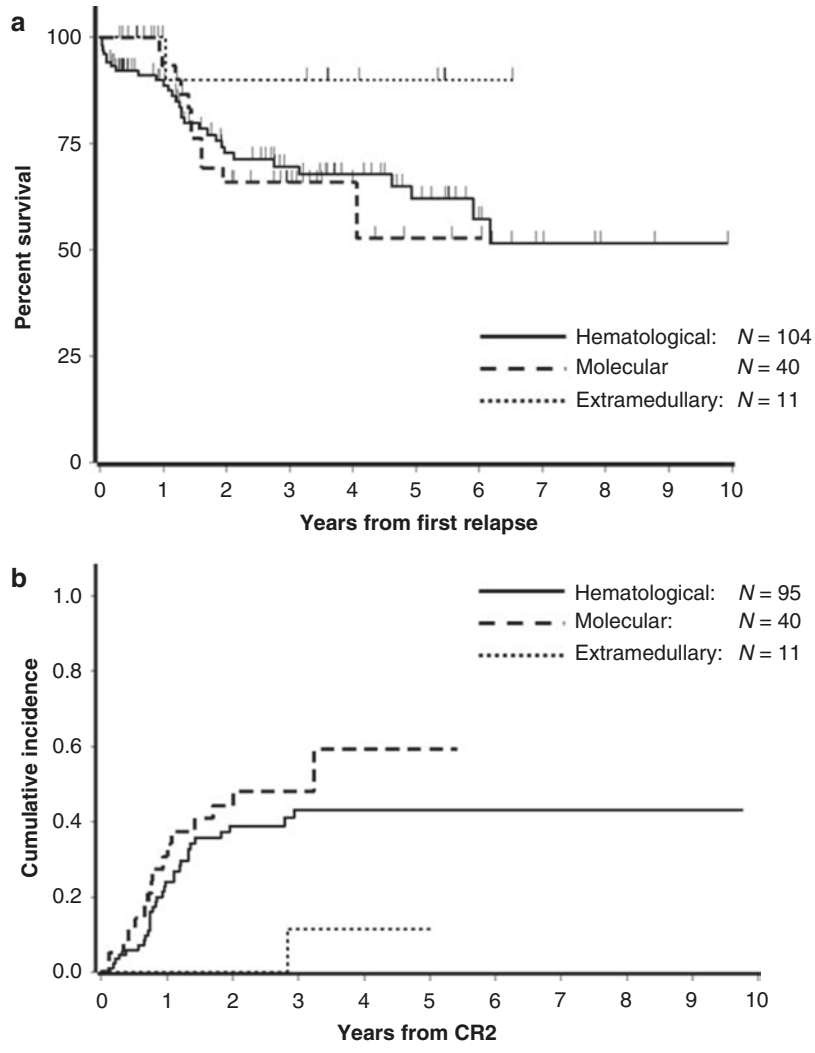

Fig. 12.2 Overall survival (**a**) and cumulative incidence of relapse (**b**) separated according to hematological, molecular, or extramedullary relapse (overall survival $p = 0.31$; cumulative incidence of relapse $p = 0.047$). Tics indicate the last follow-up of the living patients [18]

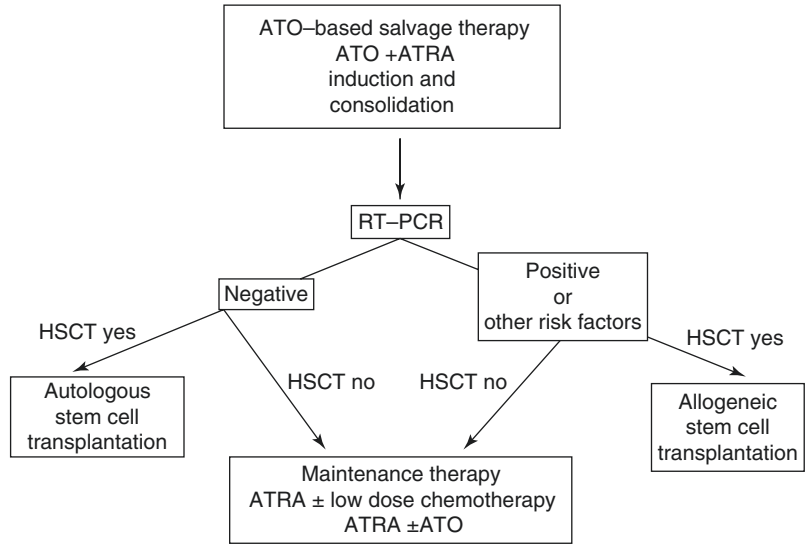

Fig. 12.3 Treatment algorithm for APL relapse. *HSCT* hematopoietic stem cell transplantation

autologous, with prolonged administration of ATO. Even if continuation of ATO therapy seems to prolong the remission duration, the majority of data suggests a longer survival after treatment intensification with autologous transplantation [26, 27].

Special Situations of Relapse

Extramedullary Relapse

Extramedullary APL relapses are rare, and most of them involve the CNS. Therapy mostly consisted of intrathecal chemotherapy (methotrexate ± Ara-C ± steroids) with or without cranial irradiation. Sporadic relapses in other locations (e.g., cutaneous, paraspinal mass, etc.) were published as case reports [28–31].

The Spanish PETHEMA group reported a 5-year cumulative incidence of 1.7% CNS relapses and a median survival of 13 months observed in 11 of 739 patients treated with ATRA and anthracyclines in the LPA96 and 99 trials. An initial high WBC count and intracranial hemorrhage at first diagnosis were independent prognostic factors for CNS relapse [32]. A combined analysis of 806 patients included in the studies of the French/European APL group and of the PETHEMA group showed a cumulative incidence of extramedullary relapse at 3 years of 1.1% (n = 10; nine in CNS, one cutaneous) compared to isolated bone marrow relapse of 15.5%, respectively. Median survival from time of extramedullary relapse was 6.7 months [33].

In the European relapsed APL registry, 11 patients in first relapse at extramedullary sites (CNS n = 9, other n = 2) were registered. Treatment consisted of ATO ± ATRA induction and consolidation with the addition of intrathecal chemotherapy. Post-consolidation therapy was variable including autologous transplantation in six cases and allogeneic transplantation in one case. The 3-year OS of these patients was 90% and the CIR 11% [18]. These results suggest an improvement of survival caused by ATO, as the drug was reported to penetrate the CNS over a broad range of plasma levels [34]. As reported by Chinese authors, arsenic concentration in the cerebrospinal fluid could be increased to the level of the peripheral blood, when intravenous mannitol was given prior to ATO administration [35].

Current Management of Advanced Relapses and Newer Treatment Options

Re-induction of remission, if possible, is still the main goal in advanced APL relapses. Despite reduced chances for another remission, patients may achieve a CR with various salvage approaches repeatedly. Patients pretreated with ATO may respond to ATO again. In those who became resistant after previous ATO therapy, mutations in the PML gene may be the underlying reason [36]. Allogeneic transplantation is currently the only curative chance for patients with advanced relapse.

Conservative treatment options include gemtuzumab ozogamicin (GO), which induced remissions in patients with several grades of molecular or hematological relapse [37, 38]. The synthetic retinoid tamibarotene (not approved in Europe) has a higher differentiation induction potential than conventional ATRA and induced remission in 58% of relapsed/refractory APL patients in an early study [39]. Recently tamibarotene monotherapy was reported to induce hematological remission in 65% and molecular remission in 21% of patients with advanced APL. The authors conclude that the efficacy of the drug warrants further studies in combination with ATO [40].

Conclusion

Despite improvement in the prognosis of relapsed APL with the introduction of ATO, the rate of subsequent relapses is still high. This requires further efforts to better define patients at risk of relapse and to improve the strategies for salvage therapy. Currently, ATO plus ATRA is the treatment of choice for patients in first relapse of APL after conventional therapy with ATRA and chemotherapy. Even in relapse after frontline therapy with

ATO, a second approach with ATO seems justified; however, the data in this setting are scarce. Treatment intensification with autologous HSCT remains an appropriate option for younger patients in molecular remission. In elderly patients with contraindications for HSCT, prolonged therapy with ATO may be an option. Patients with persistent positive RT-PCR or with higher degrees of relapse are candidates for allogeneic HSCT.

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