CORPORATE SYMPOSIUM

STRATEGIES FOR ADVANCED APL: LONG-TERM FOLLOWUP OF ARSENCE THERAPY AND NEW APPROACHES

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Introduction

The majority of patients with newly diagnosed acute promyelocytic leukemia (APL) are cured of their disease.[1-4] However, a relatively small percentage of patients, often those who present with high-risk disease, relapse. While some patients relapse at the molecular level, others do so with overt morphologic disease. With contemporary strategies, the relapse rate (RR) for low- and intermediate-risk patients at three-years appears less than 5 percent.[4] For high-risk patients, the three-year RR is approximately 20 percent. Late relapses have rarely been reported both in the pre-ATRA as well as the ATRA-era.[3,5,6] An increase in extramedullary relapses have been suggested by some anecdotal reports, but not clearly confirmed by other larger studies.[7-16]

Arsenic Trioxide for Patients with Relapsed APL

Ever since pioneering studies from China showed remarkable activity of arsenic trioxide (ATO) in patients with relapsed and refractory APL, ATO has emerged as the treatment of choice for all such patients.[17,18] In a combined cohort of 12 patients treated on an initial pilot study at Memorial Sloan Kettering Cancer Center,[19] and 40 patients subsequently treated on a multicenter study conducted in the United States,[20] the complete remission (CR) was 87% and only 2 patients (4%) had resistant disease. Of 42 patients evaluable for molecular response, after initial induction therapy and at least one consolidation course of ATO, 83% achieved a molecular CR. Twenty-six patients were in first relapse and 26 in subsequent relapse or had refractory disease. The estimated 2-year overall survival (OS) and relapse-free survival (RFS) rates for patients treated in first relapse were 77% and 58%, respectively. For patients with more advanced disease, the estimated 2-year OS and RFS were 50% and 38%, respectively. After longer follow-up with a median of estimated 39.3, the 3-year OS for all 52 patients was 53%. Some patients subsequently proceeded to receive some form of hematopoietic stem cell transplantation (HSCT) (15 of the 45 patients who achieved CR). However, 16 patients who received arsenic trioxide alone were maintained in reasonably durable remissions.[21] It is not clear that combining ATO with ATRA in the patient with relapsed disease who have previously been exposed to ATRA is better than administering ATO alone. (22) However, potential synergism in this setting may depend on the duration from the last exposure to ATRA. Both low-dose arsenic trioxide[23] as well as oral arsenic preparations appear effective.[24,25]

Hematopoietic stem cell transplantation for patients with advanced disease

Since the initial reports of successful outcome of patients with APL in second CR undergoing autologous HSCT, with reinfusion of molecularly negative cells, such a strategy has been frequently embraced.[26,27] Similarly, excellent outcomes have been demonstrated by the European APL Group.[28] Among 50 patients undergoing autologous HSCT in second CR, the 7-year RFS was 79% with a transplant-related mortality (TRM) rate of only 6%. Importantly, among the 28 patients who underwent autologous HSCT with molecularly negative cells collected before transplant, only three patients (11%) relapsed. For those patients undergoing allogeneic HSCT, the TRM was 39%. Therefore, the OS was significantly better among patients undergoing autologous HSCT compared to those undergoing allogeneic HSCT. Investigators in the European Blood and Marrow Transplant Group (EBMT) also reported a high TRM among patients undergoing allogeneic HSCT.[29] Among 17 patients with advanced APL in either second molecular CR or with persistent molecular disease, the disease-free survival (DFS) was 46% with a non-relapsed mortality rate of 32%.[30] Preliminary data from the Center for Blood and Marrow Transplant Research (CIBMTR) show better outcome after autologous HSCT compared to allogeneic HSCT for patients in second CR.

Monoclonal antibodies in patients with early relapse

Initial pilot studies suggested that the antibody M195, a mouse monoclonal antibody reactive with the antigen CD33 expressed on the cell-surface could reduce minimal residual disease in patients with relapsed APL after attaining a remission with ATRA.[31,32] Gemtuzumab Ozogamicin (GO), a humanized anti-CD33 monoclonal antibody chemically linked to the potent agent calicheamicin, appears particularly active in patients with APL. Lo-CoCo and colleagues administered GO to 16 patients in molecular relapse.[33] Molecular CR was obtained in 91% of patients after only two doses, and the remaining patients after the third dose. Further anecdotal reports confirm the apparent remarkable sensitivity in APL of GO.[34,35] Acute promyelocytic leukemia cells express CD33 strongly, but express relatively low levels of P-glycoprotein. GO has been shown to inhibit the growth of ATRA-resistant as well as ATO-resistant APL cells in a dose-dependent manner,[36] providing a rationale for combinations of all 3 agents.

Arsenic trioxide for molecular relapse of APL

In a preliminary report, two patients in molecular relapse discovered at the time of routine screening while in first CR at 12 and 36 months, became PCR negative after one cycle of ATO given in standard-dose schedule.[37] Both patients remained RT-PCR negative at six and eight months without further therapy. One patient completed 4 cycles of ATO and the second was removed after on 20 doses of the first cycle.

Novel strategies for the treatment of APL Preliminary laboratory

Preliminary laboratory studies suggest that other novel strategies may be effective in patients with APL. Approximately 30-35% of patients with APL have internal tandem duplications of the FLT3 gene.[38-41] In general, data suggests the presence of FLT3 internal tandem duplication mutations confer less favorable prognosis. There are data to suggest that internal tandem duplications of the FLT3 gene and PML/RAR· and the PML/RAR· fusion transcript cooperate in the development of APL. These data suggest that small molecules which inhibit mutations in the FLT3 gene may be useful. There are also data to suggest that increased angiogenesis may play a role in the pathogenesis of APL. Such angiogenesis appears to mediated by vascular endothelial growth factors (VEGF), but not basic fibroblast growth (bFB).[42] Furthermore, in vitro studies show that ATRA abrogates VEGF production by NB4 cells. Therefore, antiangiogenic approaches may prove beneficial. Although not currently available, an intravenous lipsomal formulation of ATRA can induce durable molecular CRs in patients with advanced disease.[43]

Summary

Patients with relapsed or refractory APL have a reasonably favorable prognosis. Arsenic trioxide has become the treatment of choice. As a single agent, molecular CR can be induced in the majority of patients. Furthermore, some

patients may enjoy durable remissions with ATO as a single agent. However, the factors that predict for such success are not known. Therefore, for patients in a second CR, HSCT has become an attractive strategy; the results of autologous HSCT when molecularly negative cells can be harvested are very encouraging. Allogeneic HSCT can be reserved for patients with persistent disease. New strategies to pursue include monoclonal antibody therapy, FLT3 inhibitors, combinations of ATRA, ATO and GO, and antiangiogenic approaches.

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ARSENIC TRIOXIDE IN RELAPSED ACUTE PROMYELOCYTIC LEUKEMIA: TREATMENT STRATEGIES AND FUTURE PROSPECTS

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Results with conventional treatment strategies in relapsed APL

There are several options in relapsed APL to induce a renewed remission.[3] Chemotherapy combinations as in first line therapy or intensified regimens as with anthracyclines and medium or high doses of ara-C, partly in combination with etoposide, have been effective. These regimens have mostly been combined with ATRA and in patients in relapse have achieved similar remission rates as in primary therapy of around 90%. However, in general these remissions were no longer stable.[1,4,11] At present the only therapeutic approach to a relapse of APL with confirmed curative potential is allogeneic PBSCT, which is the therapy of choice for patients able to receive a transplant with a compatible related or unrelated donor. In general, before an allogeneic transplant it is endeavored to achieve molecular remission. However, it was also observed that some patients, who were positive before allogeneic transplantation, became negative after transplantation.[5] In patients who do not have a donor available, with an autologous PBSCT, long-term remission or even a cure could be induced if a PCR-negative stem cell transplant was used.[6] According to the results of an assessment of the EBMT patients who after the introduction of ATRA were given an allogeneic or autologous transplant, it was shown that the allogeneic transplant was associated with greater antileukemic efficacy but also with a higher transplant-associated mortality. The result of this was that the benefit of the allogeneic transplant was partly offset.[8] It became further evident from the results of the chemotherapy studies in relapsed APL that a high toxicity of chemotherapy has a negative effect on the feasibility and the results of the transplantation.[11]

Arsenic trioxide

The mechanism of action of ATO in APL is complex and not yet known in detail. In *in vitro* studies a dual effect has been shown. At a high concentration ATO induces apoptosis. Lower concentrations lead to a partial differentiatiating-out of the cells. Antiangiogenic effects are also being discussed. In clinical studies of patients with relapsed and refractory APL, hematological and molecular remission rates of between 80 and 100% have been achieved, which indicates a high sensitivity of APL blasts to ATO. In most studies an absolute ATO dose of 10 mg per day or 0.15 mg/kg per day for up to 60 days was administered by intravenous infusion. The post-remission therapy was carried out in various ways either with further cycles of ATO, chemotherapy or a combination of the two.[2,7,9,10]

The first published study with a longer observation period over 7 to 48 months includes 33 Chinese patients with relapsed APL. Factors that had a positive effect on the remission period were a leukocyte count of less than 10000/µl at the start of the treatment with ATO (p=0.038) and the combination of ATO with chemotherapy in the post-remission therapy compared with ATO therapy on its own (p=0.01). Nevertheless, sustained remissions of up to 41+ months with ATO alone have been observed, which indicate an extensive antileukemic effect on APL blasts.[7] In the American licensing study for ATO, molecular monitoring was carried out in 40 of the 52 patients who were included. The rate of molecular remissions after an induction cycle with ATO was 50% and after consolidation with a further ATO

cycle it was 83%. The 3-year survival rate was approximately 50%.9,10 With additional chemotherapy and also with an autologous or allogeneic transplantation, the relapse-free survival was extended compared with ATO therapy alone. The results also indicate that with the use of ATO for the induction of remission, the toxicity of chemotherapy can be avoided and as a result a positive effect on the feasibility of the transplantation was achieved. ATO is generally well tolerated. Potentially dangerous side-effects are a prolongation of the QT interval in the ECG with the possible consequence of life-threatening ventricular tachycardia and leukocyte activation syndrome, which occurs in about 25% of patients.

Strategy for managing patients with relapsed APL

The results of the different forms of therapy indicate that it is possible in different ways to treat successfully relapses in APL. The relative rarity of relapses and the only small numbers of patients in the series published, often with only a short observation period, make it difficult to compare the individual therapeutic approaches. Of the available alternatives to chemotherapy, ATO (TRISENOX) is now used the most frequently and has been licensed in the USA and Europe for the treatment of relapsed APL. Against the background of the relatively high toxicity of chemotherapy and the relatively good tolerability of ATO with a high rate of efficacy, the question arises as to what extent the use of traditional chemotherapy or its intensification can be dispensed with if ATO is used. This applies in particular also to allogeneic or autologous transplantation. Due to the rarity of APL relapses it is difficult to carry out a randomized study. It is therefore the objective of the prospective controlled study proposed here to use the therapeutic strategy most suited for the individual including ATO, within an established approach.

Treatment strategy for relapsed APL (Figure 1)

After remission induction with ATO (first ATO cycle) and consolidation therapy (second ATO cycle), criteria that play a part in deciding the therapy for the individual are:

- 1. the feasibility of an allogeneic PBSCT
- 2. the feasibility of an autologous PBSCT
- 3. contraindication to intensive chemotherapy
- 4. the PCR status of the patient and any autologous stem cell transplant.

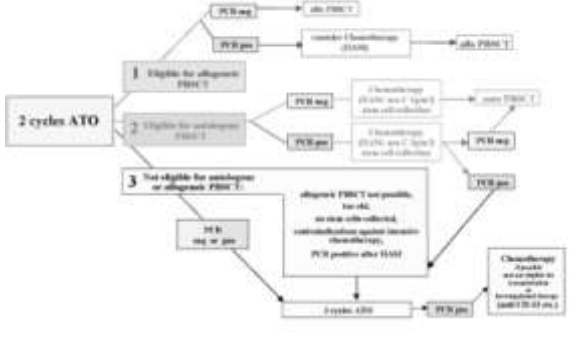

Figure 1. Treatment Strategy for Relapsed APL.

Achieving molecular remission (negative nested RT-PCR of PML-RARα, sensitivity 10-4) by ATO should enable patients with a planned allogeneic PBSCT to dispense with chemotherapy before the transplant (avoiding toxicity) and consider intensive chemotherapy only to PCR-positive patients with the objective in this way of achieving molecular remission. In patients in whom an allogeneic transplantation is not possible but who are suitable for an autologous PBSCT, the intensity of the chemotherapy needed for collecting stem cells could be stratified according to the results of the PCR. Here, in the case of molecular remission after ATO it would be a matter of choosing a higher dose of chemotherapy, and in the case of a positive PCR of choosing a lower dose of chemotherapy (HAM with ara-C individual dose 3 vs. 1g/m^2). In patients who do not qualify for one of these transplantation methods, the clinical and molecular effectiveness of a therapy with ATO without the additional use of chemotherapy should be evaluated. This strategy should include a smaller number of patients, who while they do not qualify for an autologous transplantation, have no contraindication against intensive chemotherapy. Chemotherapy (HAM) should then be administered to these patients if molecular remission is not achieved with 3 cycles of ATO or if a molecular relapse occurs. Concomitant molecular monitoring by means of qualitative and quantitative PCR should enable the individual kinetics of the MRD to be recorded as a function of the individual therapy stages and the stratification of the therapy to be organized accordingly. Patients in whom after the conclusion of the strategy used individually, no PCR-negativity has been achieved, or who relapse again, can be treated further outside the study with experimental therapeutic approaches (e.g. with antibodies against CD33 etc.). In Germany this protocol is active since January 2005. There are also efforts of the European APL Group to establish a common protocol for relapsed APL on the basis of a similar approach.

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WORKSHOP I
THE ACUTE PROMYELOCYTIC LEUKEMIA ASSOCIATED COAGULOPATHY

PROCOAGULANT SURFACE OF LEUKEMIC BLASTS

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Patients with acute leukemia generally exhibit activation of the coagulation system, and individuals with acute promyelocytic leukemia (APL) particularly are at high risk for severe thrombotic and bleeding complications due to hemostatic changes.

A retrospective study reported on the hemorrhagic and thrombotic events at presentation and during induction in 34 consecutive APL patients treated in a single referral center.[1] The most consistent hemostatic abnormality was decreased fibrinogen level (<150 mg/dL) found in 21 patients (61%), Life-threatening bleeding manifestations occurred in 10 patients (29%). However, by a multivariate analysis, severe bleeding complications did not correlate with hemostatic parameters but did correlate with white cell count at presentation. Four patients (12%) had severe thrombotic events, two cerebral sagital sinus thrombosis, one pulmonary embolism, and one subclavian vein thrombosis. Two other patients had pseudotumor cerebri. Three out of six patients with thrombotic events were found to have thrombophilia. Thus the hemostatic parameters were not helpful in predicting neither hemorrhage nor thrombosis in APL patients, while results may suggest an association between thrombophilia and thrombosis in APL patients.

Cell surface proteins that are capable of procoagulant effect include tissue factor (TF) and protease-activated receptor-1 (PAR-1). Cell surface proteins that have either an anticoagulant or a profibrinolytic effect include tissue factor pathway inhibitor (TFPI) and urokinase plasminogen activator receptor (uPAR). uPAR is a specific cellular receptor to the urokinase. plasminogen activator (uPA) resulting in the enhanced activation of plasminogen. Over-expression of TF, cancer procoagulant, and acquired activated protein C resistance[2] have been argued as main factors for the coagulopathy in malignant disorders.

Expression of coagulation proteins on leukemic blast membranes can determine the local hemostatic balance and may correlate with thrombotic manifestations.

Several groups evaluated cell surface expression of TF alone on leukemic cells.[3,4] Lopez-Pedrera *et al.*[5] studied by flow-cytometry the cell surface expression of both TF and uPAR in 26 acute leukemia patients. In that study, TF level was found to be high (>68%) in 2 out of 4 patients with AML-M3 and in all the 3 patients with AML-M5, whereas in patients with other subtypes of leukemia TF value was <16%. uPAR expression was high (92%) in one of the four AML-M3 patients and in one of the AML-M5 patients (70%); the other two AML-M5 patients were not evaluated. In the rest of the patients the uPAR expression was less than 17%.

In a recent study we have included 51 consecutive patients with newly diagnosed acute leukemia (25 AML-M0-2, 11 AML-M3, 6 AML-M4-5, 9 ALL), who were followed up prospectively for thrombotic manifestations during the first month since diagnosis.[6] Thrombotic manifestations were present in 13 out of 51 (26%) patients: 6 out of 25 patients (24%) with AML-M0-2 and 7 out of 11 patients (64%) with