GERMAN INTERGROUP RECOMMENDATIONS ON THE DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF ACUTE PROMYELOCYTIC LEUKEMIA (APL)

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<table>
<thead>
<tr>
<th><strong>Glossary</strong></th>
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<tr>
<td>AML</td>
<td>acute myeloid leukemia</td>
</tr>
<tr>
<td>APL</td>
<td>acute promyelocytic leukemia</td>
</tr>
<tr>
<td>aPTT</td>
<td>activated partial prothrombin time</td>
</tr>
<tr>
<td>Ara-C</td>
<td>cytarabine</td>
</tr>
<tr>
<td>ATO</td>
<td>arsenic trioxide</td>
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<tr>
<td>ATRA</td>
<td>all-trans retinoic acid</td>
</tr>
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<td>Bone marrow puncture</td>
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<td>CD</td>
<td>cluster of differentiation</td>
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<td>CR</td>
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</tr>
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<td>Case report forms</td>
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<td>CRm</td>
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<td>disseminated intravascular coagulation</td>
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<td>French-American-British classification</td>
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<td>FISH</td>
<td>fluorescence in-situ hybridization</td>
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<td>Gpt</td>
<td>gigaparticles</td>
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<td>hCR</td>
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</tr>
<tr>
<td>ITD</td>
<td>internal tandem duplication</td>
</tr>
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<td>MRD</td>
<td>minimal residual disease</td>
</tr>
<tr>
<td>NUMA</td>
<td>nuclear mitotic apparatus</td>
</tr>
<tr>
<td>OS</td>
<td>overall survival</td>
</tr>
<tr>
<td>PML-RARα</td>
<td>promyelocytic retinoid acid</td>
</tr>
<tr>
<td>POX</td>
<td>peroxidase</td>
</tr>
<tr>
<td>QoL/QLQ</td>
<td>quality of life/ quality of life</td>
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<td>RDM</td>
<td>molecular resistant disease</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>reverse transcriptase polymerase chain reaction</td>
</tr>
<tr>
<td>HSCT</td>
<td>hematopoietic stem cell transplantation</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood counts</td>
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<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
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1 DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF PATIENTS WITH APL

1.1 Definition of APL

Acute promyelocytic leukemia (APL) is considered a rare disease with estimated 200 to 300 newly-diagnosed cases per year in Germany. According to the FAB classification APL is designated as "M3 leukemia" and assigned to the WHO defined type of AML with recurrent cytogenetic abnormalities, "acute promyelocytic leukemia with t(15;17)(q22;q11), (PML/RARα) and variants". Detection of PML-RARα fusion is carried out by conventional cytogenetics including fluorescence in situ hybridization (FISH) and/or RT-PCR. Alternative fusion partners are the zinc finger (PLZF), the nucleophosmin gene (NPM), the nuclear mitotic apparatus (NUMA) or the STAT5b gene. These fusion partners may be of therapeutic relevance, e.g. for the sensitivity to all-trans-retinoic-acid (ATRA), which does not exist with the involvement of the PZLF gene [t(11;17)(q23;q21)].

APL is often clinically characterized by the presence of coagulative abnormalities\(^1\), including disseminated intravascular coagulation (DIC), hyperfibrinolysis and unspecific proteolysis.

In up to 45 % of cases mutations of the FLT3 gene with an internal tandem duplication (ITD) of the juxtamembranous domain and point mutations in the tyrosine kinase domain II can be detected\(^2\), although their independent prognostic impact has not been demonstrated. Both mutations are correlated with higher leukocyte counts while a FLT3-ITD mutation is associated with the M3v subtype and the S-type PML/RARαprotein.

In addition to age, the most important prognostic factor is the leukocyte count at diagnosis which divides patients into a high risk (> 10 Gpt / l) and a non-high-risk group (≤ 10 Gpt / l). Through use of a risk-guided therapeutic approach the outcome of patients within both groups including risk of relapse has become almost comparable\(^3-5\).

1.2 Diagnostics of APL

The vast majority of APL cases mostly display a characteristic abnormal hypergranulation of blasts\(^6-8\). The nuclei of the cells vary in shape and size, being often bilobulated and kidney-shaped. Cytoplasm of the cells is completely filled with densed and partially condensed granulation. In some cells the cytoplasm is filled with dust granulation. Cells with characteristic bundles of Auer rods are found in the bone marrow or in the peripheral blood, the so called Faggot-cells. The M3v, however, contains fewer cells with hypergranulations or bundles of Auer rods. Hypergranulated promyelocytes strongly react with POX, SSB und chloracetate esterase. The expression of CD33, CD117 and absence of HLA-DR and CD34 on the surface of APL blasts is characteristic of the disease.

The t(15;17) translocation and the respective PML-RARα fusion transcript are diagnostically conclusive and represent definitive hallmarks of APL diagnosis\(^7-9\). According to the current WHO classification cases with specific cytogenetic and molecular genetic aberrations e.g. t(15;17)(q22;q11-12) resulting in the fusion transcript PML/RARα- are classified as AML independently of the percentage of blasts in the bone marrow and peripheral blood\(^9\).
The molecular analysis for the detection of the promyelocytic retinoic acid receptor α (PML-RAR α) fusion gene is carried out by a reverse transcriptase-polymerase chain reaction (RT-PCR). This method provides a fast and a highly sensitive verification of the initial diagnosis and of minimal residual disease (MRD) in the course of APL therapy. The results of several independent studies have shown that a positive detection of PCR transcripts for PML-RARα hybrid gene during cytomorphological remission within consolidation cycles is a predictive factor for an early hematological recurrence, whereas an abiding negative PCR in the bone marrow is usually associated with long-term survival and cure after therapy (also in patients with relapse)\textsuperscript{10,11}.

1.3 Therapeutic approaches in APL

APL disease must be classified as an emergency with immediate initiation of supportive therapy. In the case of morphological and clinical suspicion of APL, therapy must be started immediately before a genetic diagnosis is available because of the potential lethal complications and the possibility of a curative therapy. Prior to therapy a bone marrow and blood diagnostic is essential. First-line treatment recommendations differ for patients of the high-risk group and the non-high-risk group according to the Sanz Score which are defined as follows\textsuperscript{5}:

\[
\begin{array}{ll}
\text{WBC in high-risk group} & \text{WBC in non-high-risk group} \\
> 10 \text{ Gpt} / \text{l} & \leq 10 \text{ Gpt} / \text{l}
\end{array}
\]

1.3.1 ATRA-based induction therapy

Anthracylidine and Ara-C-based combination chemotherapy were used until the 1980s and complete remission rates (CR) of up to 80 % were achieved. However, disease recurrences were observed in two thirds of the patients. Furthermore, this therapy was associated with a high rate of early death due to toxicity and bleeding\textsuperscript{12-15}.

The introduction of all-trans retinoic acid (ATRA) significantly changed therapeutic success in APL patients. ATRA causes differentiation of abnormal promyelocytes to mature neutrophils \textit{in vitro} and \textit{in vivo}. Complete remission rates were achieved with single agent ATRA in up to 80-90 % of newly-diagnosed and relapsed patients with APL\textsuperscript{16-21}. Furthermore, ATRA rapidly alleviates the disturbed coagulation cascade. However, the accelerated differentiation to mature neutrophils often induces a rapid increase of leukocytes. In fact, in 15-20 % of patients an ATRA- or better “differentiation-syndrome” can occur which is associated with a high mortality rate\textsuperscript{22-25}.

The duration of remission with single agent ATRA therapy however was often not enduring\textsuperscript{16,17}. Therefore, concepts with combined and concomitant administration of ATRA and intensive chemotherapy were explored\textsuperscript{26,27}. These studies consistently showed a higher CR rate (>95 %) compared to conventional chemotherapy as well as prolonged remission.
duration in either randomized or historical comparisons\textsuperscript{28-37}. The most widely used combination for induction therapy irrespective of APL risk is the combination of ATRA plus Idarubicin (AIDA).

1.3.2 Consolidation therapy

Molecular remissions can be achieved in more than 90 % of patients if at least two anthracycline-containing consolidation therapies are used. Therefore, this is considered the present therapeutic standard for all patients with APL in CR after induction chemotherapy\textsuperscript{38}. There is no comparative study on the efficacy of ATRA in addition to chemotherapy during consolidation. However, historical comparisons have demonstrated that incorporation of ATRA contributed to improved outcome\textsuperscript{27,39}.

The role of Ara-C in APL has long been controversial. However, comparative cohort studies in high-risk patients (WBC > 10 Gpt / l) show a clearly positive effect with a significant higher remission rate, better disease-free and overall survival rate in favour of Ara-C-based therapy during consolidation\textsuperscript{6,27,35}.

1.3.3 Maintenance therapy

In the European APL-93 study it was shown that a three-fold maintenance therapy with ATRA, 6-mercaptopurine and methotrexate results in a lower recurrence rate, especially in patients with high white blood cell count at diagnosis. However, this study did not differ between patients according to the PCR-status after consolidation\textsuperscript{31}. Furthermore, no advantage of maintenance therapy in patients who tested negative after consolidation was observed by the Italian GIMEMA group\textsuperscript{40}. Therefore, maintenance therapy is based on a relatively low level of evidence. Despite these controversial results, maintenance therapy is still included in the most ATRA-plus-chemotherapy-based protocols.

Due to the high cure rate with ATRA and chemotherapy in APL, there is no indication for hematopoietic stem cell transplantation (HSCT) in patients who are in first molecular remission after completion of consolidation therapy.

1.3.4 Treatment of minimal residual disease (MRD) or relapse

Despite successful first-line treatment approximately 10-15 % of patients relapse. In case of persistence of minimal residual disease (MRD) with PML/RARα detection or molecular or hematological relapse, treatment with arsenic trioxide (ATO) +/- ATRA for induction and consolidation therapy is the treatment of choice. This should be followed by further post consolidation therapy. Autologous HSCT after high-dose therapy probably contributes to the stabilization of remission, provided that PML/RARα is negative by PCR in the autologous graft and in the patient bone marrow prior to transplantation\textsuperscript{41-46}. In patients not achieving clearance of MRD by conventional therapy including ATO an allogeneic HSCT should be considered.
1.3.5 ATO in APL

ATO is the most effective single agent in APL\(^{47}\). ATO acts via complex mechanism in APL that is not yet fully explained. At a high concentration (0.5 to 2.0 \(\mu\)mol/l) ATO induces apoptosis \textit{in vitro}, while at lower concentrations (0.1 to 0.5 \(\mu\)mol/l) it induces partial differentiation of leukemic promyelocytes through PML/RAR\(\alpha\) degradation and inhibits angiogenesis\(^{48-51}\).

ATO is licensed for the treatment of relapsed and refractory APL in the USA and Europe\(^{44,45,52-58}\) and can achieve remission rates in up to 90\% of patients. Concerning its toxicity profile, ATO is usually well tolerated and its use is associated with a series of manageable adverse events (hyperleucocytosis, increase of liver enzymes, APL differentiation syndrome, prolongation of the QT interval\(^{59}\)). Most of the adverse events mentioned above are usually mild and manageable\(^{44,58}\).

The antileukemic efficiency of ATO is increased when combined with ATRA. ATO as single agent is able to induce durable molecular remission after two cycles in the majority of patients treated for disease recurrence\(^{57}\). Results of various studies conducted with ATO as single agent or combined with ATRA for newly diagnosed APL patients reported CR rates of 86-95\%, molecular remission rates after two cycles of 76-100\% and survival rates of 86-88\%, with significantly better responses being obtained in patients with non-high risk disease as compared to high-risk patients\(^{60-64}\). Recent data of the APL0406 – Intergroup Study (GIMEMA – AML-SG/SAL) showed that ATO plus ATRA is at least as effective as AIDA-based therapy as first-line treatment in non-high risk APL patients\(^{65}\). In particular, early mortality was almost absent in the experimental treatment arm combining ATO and ATRA. In addition, the results of a recent published randomized trial evaluating ATO in first-line therapy during consolidation demonstrated that ATO further reduced the risk of recurrence and improved survival\(^{66}\).

1.4 Intergroup guidelines for the treatment of APL

APL is a highly curable malignancy. Once regarded as the most aggressive and rapidly fatal human leukemia, APL has become over the past 2 decades a curable disease, with more than 80\% of patients now being long-term survivors. However, treatment of APL is still challenging, in particular during induction therapy, and high rates of cure can only be achieved in centers with well trained staff. Therefore, treatment in highly specialized and experienced centers is mandatory including standardized procedures. The recommendations on APL diagnostics and therapy of newly diagnosed and relapsed APL are based on national (http://www.dgho-onkopedia.de/de/onkopedia/leitlinien/akute-promyelozytaere-leukaemie) and European (ELN) guidelines\(^{38}\) (http://www.leukemia-net.org/content/leukemias/aml/apl/apl_recommendations/index_eng.html).

The detailed German intergroup treatment guidelines are provided below (Figure 1) and depend on the leukocyte counts at initial diagnosis (see 1.3).
FIGURE 1: OVERVIEW OF TREATMENT RECOMMENDATIONS FOR NEWLY DIAGNOSED APL
FIGURE 2: OVERVIEW OF RECOMMENDATIONS FOR MOLECULAR RESISTANT OR RELAPSED PATIENTS

* for details of consolidation and postconsolidation therapy and list of options see ELN website:
http://www.leukemia-net.org/content/leukemias/aml/apl/apl_recommendations/index_eng.html
1.4.1 Treatment recommendation for high-risk APL (WBC >10 Gpt/l at initial diagnosis) according to AIDA

1.4.1.1 INDUCTION THERAPY (HIGH-RISK APL)\(^5\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA</td>
<td>45 mg/m(^2)</td>
<td>p.o. in two single doses</td>
<td>daily</td>
<td>until CR, max. 60 days; doses will be rounded-up to next 10 mg increment</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>12 mg/m(^2)</td>
<td>i.v.</td>
<td>day 1, 3, 5, 7</td>
<td>only 3 days in elderly and comorbid patients</td>
</tr>
</tbody>
</table>

- prophylaxis of APL differentiation syndrome with prednisone 0.5 mg / kg / day p.o. from day 1 of ATO application to the end of induction therapy and possibly hydroxyurea (see 2.1) when leucocytes further raise up to > 10 Gpt / l
- bone marrow puncture on day 28
- induction therapy should be terminated on the basis of morphological criteria (if CR or CRi is reached on day 28)
- in case of not achieving CR or CRi on day 28, ATRA therapy should be continued up to max. day 60 until terminal differentiation is reached; this should be accompanied by serial bone marrow assessments to definitively demonstrate CR
- cytogenetic and molecular assessment at the end of induction therapy has no value in case of CR. Molecular responses should be assessed after consolidation only

1.4.1.2 CONSOLIDATION THERAPY (HIGH-RISK APL)

After achieving a hematological CR after induction therapy, 3 courses of ATRA plus chemotherapy are intended. Start of consolidation cycles is considered after hematological recovery with neutrophils \(\geq 1.0\) Gpt / l and platelets \(\geq 100\) Gpt / l. In case of morphological CR and regenerated blood counts, consolidation therapy should be started within 4 weeks after documented CR. Each course of therapy should be initiated at hematological recovery from the previous course. The PCR status after the end of consolidation is an important stratification parameter for the subsequent therapy.
### 1. Consolidation therapy - high-risk APL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA</td>
<td>45 mg/m²</td>
<td>p.o. in two single doses</td>
<td>days 1-15</td>
<td>doses will be rounded-up to next 10 mg increment</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>5 mg/m²</td>
<td>i.v.</td>
<td>day 1, 2, 3, 4</td>
<td>prior to Ara-C administration</td>
</tr>
<tr>
<td>Ara-C</td>
<td>1000 mg/m²</td>
<td>i.v. over 3h</td>
<td>day 1, 2, 3, 4</td>
<td>after the end of Idarubicin</td>
</tr>
</tbody>
</table>

### 2. Consolidation therapy - high-risk APL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA</td>
<td>45 mg/m²</td>
<td>p.o. in two single doses</td>
<td>days 1-15</td>
<td>doses will be rounded-up to next 10 mg increment</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>10 mg/m²</td>
<td>i.v.</td>
<td>day 1, 2, 3, 4, 5</td>
<td></td>
</tr>
</tbody>
</table>

### 3. Consolidation therapy - high-risk APL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA</td>
<td>45 mg/m²</td>
<td>p.o. in two single doses</td>
<td>days 1-15</td>
<td>doses will be rounded-up to next 10 mg increment</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>12 mg/m²</td>
<td>i.v.</td>
<td>day 1</td>
<td>prior to Ara-C administration</td>
</tr>
<tr>
<td>Ara-C</td>
<td>150 mg/m²/8h</td>
<td>i.v.</td>
<td>day 1, 2, 3, 4, 5</td>
<td></td>
</tr>
</tbody>
</table>

During all consolidation cycles (1-3) the following diagnostics are recommended:

- bone marrow samples should be collected with regenerated blood counts before the start of second and third consolidation cycle as well as after the last consolidation cycle and should be tested for morphology and by RT-PCR for assessment of molecular remission.
• patients without molecular remission at the end of the entire consolidation program will be considered as molecularly resistant (see 1.4.4)

Intracranial prophylaxis before each consolidation cycle is not recommended in general, but may be considered in high risk patients, according to local guidelines.

1.4.1.3 MAINTENANCE THERAPY (HIGH-RISK APL)

The clinical benefit of maintenance therapy is of lower evidence according to recent studies^{28;33;40} and should be initiated only in patients who are in a molecular remission (PML-RARα-negative in the bone marrow).

The start of maintenance therapy is one month (up to a maximum of 3 months) after consolidation therapy if neutrophils are ≥ 1.0 Gpt/l and platelets are ≥ 100 Gpt/l. The duration of maintenance therapy is a total period of 2 years. During this time, patients receive 7 courses with 6-mercaptopurine and methotrexate (each lasting 3 month) and 6 courses of ATRA for 15 days.

The last cycle ends with the administration of 6-mercaptopurine and methotrexate.

### Maintenance therapy – high-risk APL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Mercaptopurine</td>
<td>50 mg/m²</td>
<td>p.o.</td>
<td>daily (day 1-91) followed by 15 days of rest</td>
<td>for 7 cycles; rounded down to the nearest 10 mg increment</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>15 mg/m²</td>
<td>i.m./p.o.</td>
<td>once weekly for 91 days followed by 15 days of rest</td>
<td>for 7 cycles</td>
</tr>
<tr>
<td>ATRA</td>
<td>45 mg/m²</td>
<td>p.o. in two single doses</td>
<td>daily for 15 days (prior to day 1 or after day 91)</td>
<td>every 3 month for a total of 6 cycles; during ATRA therapy treatment break of 6-MP und MTX</td>
</tr>
</tbody>
</table>

Consider cotrimoxazol as pneumocystis prophylaxis
• bone marrow samples should be collected with regenerated blood counts at the beginning of each maintenance cycle as well as after the last maintenance cycle and should be tested for morphology and by RT-PCR for assessment of molecular remission

1.4.1.4 DOSE MODIFICATIONS

Dose modifications of ATRA and conventional chemotherapeutic agents (mitoxantrone, idarubicine, methotrexate and 6-mercaptopurine) should be performed according to the SMPC.

In case of ATRA-induced non-hematological toxicities (grade 3/4 according to CTCAE Version 4.0) the following dose modifications are recommended:

<table>
<thead>
<tr>
<th>Dose level</th>
<th>0 (Start level)</th>
<th>-1</th>
<th>-2</th>
<th>-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA [mg/m²]</td>
<td>45</td>
<td>37.5</td>
<td>25</td>
<td>20</td>
</tr>
</tbody>
</table>

In general, as soon as the symptoms and the patients’ clinical conditions improve, the treatment with conventional chemotherapeutic agents should be resumed at 50 % of the previous dose. Thereafter, in the absence of worsening of the previous toxicity, conventional chemotherapeutic agents should be resumed at full dosage. In the case of the reappearance of symptoms, conventional chemotherapeutic agents should be reduced to the previous dosage.

1.4.2 Treatment recommendation for non-high-risk APL (WBC ≤10 Gpt/l at initial diagnosis) according to AIDA

1.4.2.1 INDUCTION THERAPY

The induction therapy will be conducted according to the treatment recommendations for patients of the high-risk group.
**Induction therapy - non-high-risk APL**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA</td>
<td>45 mg/m²</td>
<td>p.o. in two single doses</td>
<td>daily</td>
<td>until CR, max. 60 days; doses will be rounded-up to next 10 mg increment</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>12 mg/m²</td>
<td>i.v.</td>
<td>day 2,4,6,8</td>
<td>only 3 days in elderly and comorbid patients</td>
</tr>
</tbody>
</table>

- prophylaxis of APL differentiation syndrome with prednisone 0.5 mg / kg / day p.o. from day 1 of ATO application to the end of induction therapy and possibly hydroxyurea (see 2.1) when leucocytes raise up to > 10 Gpt / l
- bone marrow puncture on day 28
- induction therapy should be terminated on the basis of morphological criteria (if CR or CRi is reached on day 28)
- in case of not achieving CR or CRi on day 28, ATRA therapy should be continued up to max. day 60 until terminal differentiation is reached; this should be accompanied by serial bone marrow assessments to definitively demonstrate CR
- cytogenetic and molecular assessment at the end of induction therapy has no value in case of CR. Molecular responses should be assessed after consolidation only

### 1.4.2.2 CONSOLIDATION THERAPY

After achieving a hematological CR after induction therapy, 3 courses of ATRA plus chemotherapy are intended. Start of consolidation cycles is considered after hematological recovery with neutrophils ≥ 1.0 Gpt / land platelets ≥ 100 Gpt / l. In case of morphological CR and regenerated blood counts, consolidation therapy should be started within 4 weeks after documented CR. Each course of therapy should be initiated at hematological recovery from the previous course. The PCR status after the end of consolidation is an important stratification parameter for the subsequent therapy.
### 1. Consolidation therapy – non-high-risk APL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA</td>
<td>45 mg/m²</td>
<td>p.o. in two single doses</td>
<td>days 1 - 15</td>
<td>doses will be rounded-up to next 10 mg increment</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>5 mg/m²</td>
<td>i.v.</td>
<td>day 1, 2, 3, 4</td>
<td></td>
</tr>
</tbody>
</table>

### 2. Consolidation therapy – non-high-risk APL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA</td>
<td>45 mg/m²</td>
<td>p.o. in two single doses</td>
<td>days 1 - 15</td>
<td>doses will be rounded-up to next 10 mg increment</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>10 mg/m²</td>
<td>i.v.</td>
<td>day 1, 2, 3, 4, 5</td>
<td></td>
</tr>
</tbody>
</table>

### 3. Consolidation therapy – non-high-risk APL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA</td>
<td>45 mg/m²</td>
<td>p.o. in two single doses</td>
<td>days 1 - 15</td>
<td>doses will be rounded-up to next 10 mg increment</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>12 mg/m²</td>
<td>i.v.</td>
<td>day 1</td>
<td></td>
</tr>
</tbody>
</table>

During all consolidation cycles (1-3) the following diagnostics are recommended:

- bone marrow samples should be collected with regenerated blood counts before the start of second and third consolidation cycle as well as after the last consolidation cycle and should be tested for morphology and by RT-PCR for assessment of molecular remission
- patients without molecular remission at the end of the entire consolidation program will be considered as molecular resistant (see 1.4.4)

An intracranial prophylaxis before each consolidation cycle is not recommended in general.

#### 1.4.2.3 MAINTENANCE THERAPY

Maintenance therapy is provided in section 1.4.1.3

#### 1.4.2.4 DOSE MODIFICATIONS

Dose modifications are provided in section 1.4.1.4.
1.4.3 Treatment recommendation for non-high-risk APL (WBC ≤10 Gpt/l at initial diagnosis) according to the APL0406 study

Recently, the APL0406 study provided evidence that the combination of ATO and ATRA is at least as effective as the AIDA regimen\(^6\), while sparing mainly hematological toxicity. In fact, there was even an improvement in survival with the ATO/ATRA arm. Therefore, this regimen was included here since physicians might consider it for their patients although ATO has only marketing authorization in the EU for relapsed APL.

1.4.3.1 INDUCTION THERAPY

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATO</td>
<td>0.15 mg/kg</td>
<td>i.v. over 2 h</td>
<td>daily</td>
<td>starting on day 1; until CR, max. 60 days</td>
</tr>
<tr>
<td>ATRA</td>
<td>45 mg/m(^2)</td>
<td>p.o. in two single doses</td>
<td>daily</td>
<td>starting on day 1; until CR, max. 60 days; doses will be rounded-up to next 10 mg increment</td>
</tr>
</tbody>
</table>

- prophylaxis of APL differentiation syndrome with prednisone 0.5 mg / kg / day p.o. from day 1 of ATO application to the end of induction therapy and possibly hydroxyurea (see 2.1) when leucocytes raise up to > 10 Gpt / l
- bone marrow puncture on day 28
- induction therapy should be terminated on the basis of morphological criteria (if CR or CRi is reached on day 28)
- in case CR or CRi is not achieved by day 28, ATO/ATRA therapy should be continued up to max. day 60 until terminal differentiation is reached; this should be accompanied by serial bone marrow assessments to definitively demonstrate CR
- cytogenetic and molecular assessment at the end of induction therapy has no value in case of CR. Molecular responses should be assessed after consolidation only
1.4.3.2 CONSOLIDATION THERAPY

ATO/ATRA-based induction therapy is followed by 4 courses of ATO/ATRA-based consolidation. Start of consolidation cycles is considered after hematological recovery with neutrophils \( \geq 1.0 \text{ Gpt} / l \) and platelets \( \geq 100 \text{ Gpt} / l \). In case of morphological CR and regenerated blood counts, consolidation therapy should be started within 4 weeks after documented CR. Each course of therapy should be initiated at hematological recovery from the previous course. The PCR status after the end of consolidation is an important stratification parameter for the subsequent therapy.

### Consolidation therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATO</td>
<td>0.15 mg/kg</td>
<td>i.v. over 2 h</td>
<td>daily for 5 days a week; treatment break on day 6 and 7</td>
<td>4 weeks on 4 weeks off for a total of 4 courses; last cycles will be administered on week 25-28</td>
</tr>
<tr>
<td>ATRA</td>
<td>45 mg/m²</td>
<td>p.o. in two single doses</td>
<td>daily</td>
<td>14 days on, 14 days off for a total of 7 courses; doses will be rounded-up to next 10 mg increment</td>
</tr>
</tbody>
</table>

Dose-modifications in case of toxicities (e.g. liver, QTc time) should be made according to SmPC (attached in section 1.4.3.3).

During all consolidation cycles (1-4) the following diagnostics are recommended:

- bone marrow samples should be collected with regenerated blood counts before the start of second, third and fourth consolidation cycle as well as after the last consolidation cycle and should be tested for morphology and by RT-PCR for assessment of molecular remission
- patients without molecular remission at the end of the entire consolidation program will be considered molecularly resistant and should be offered conventional chemotherapy (e.g. AIDA) followed by an autologous or allogeneic HSCT (see figure 2).
1.4.3.3 Dose modifications

In case of non-hematological toxicities (grade 3/4 toxicities according to CTCAE Version 4.0) of ATO and ATRA (e.g. QT prolongation, differentiation syndrome, hepatotoxicity, pseudotumor cerebri) the following dose modifications are recommended:

<table>
<thead>
<tr>
<th>Dose level</th>
<th>0 (Start level)</th>
<th>-1</th>
<th>-2</th>
<th>-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATO [mg/kg]</td>
<td>0.15</td>
<td>0.11</td>
<td>0.10</td>
<td>0.075</td>
</tr>
<tr>
<td>ATRA [mg/m²]</td>
<td>45</td>
<td>37.5</td>
<td>25</td>
<td>20</td>
</tr>
</tbody>
</table>

As soon as the symptoms and the patients’ clinical conditions improve, the treatment with ATRA and/or ATO should be resumed at 50 % of the previous dose during the first 7 days after the disappearance of the symptoms. Thereafter, in the absence of worsening of the previous toxicity, ATRA and/or ATO should be resumed at full dosage. In the case of the reappearance of symptoms, ATRA and ATO needs to be reduced to the previous dosage.

1.4.4 Salvage therapy

Patients with molecular resistance or relapse (hematological or molecular) should be treated according to the European recommendation for salvage therapy of relapsed APL (Figure 2), which is available via the website of the European LeukemiaNet (http://www.leukemia-net.org/content/leukemias/aml/apl/apl_recommendations/index_eng.html).

In fact, due to its high anti-leukemic efficiency and low toxicity profile ATO is currently considered to be the treatment of choice in molecular or hematological relapse of APL or primary refractory patients. Concerning molecular or hematological relapse or persistence or reappearance of PCR positive after frontline therapy with ATRA-plus-chemotherapy, an early intensified ATO/ATRA-based salvage is the treatment of choice. Usually induction therapy should be performed by a course of ATO, followed by one to 4 cycles of consolidation and should be combined with ATRA.

Whether this applies as well to patients with previous ATO exposure (e.g. within the APL0406 study) is unknown. Limited data suggest a loss of efficacy of ATO salvage after ATO frontline67. Therefore an ATRA-plus-chemotherapy-based salvage (see 1.4.1.1) might be considered. Patients with subsequent molecular remission in the bone marrow and the stem cell graft probably benefit from an autologous transplantation while an allogeneic transplantation should be performed in case of persistence of PML-RARα MRD. However, long term remissions are observed with prolonged ATO treatment as well.
2 SUPPORTIVE MANAGEMENT OF APL

APL is an acute vital threat to the patient often caused by a severe plasma coagulation disorder that can be increased by the introduction of conventional therapy.\(^6^8\)

2.1 Treatment of leukocytosis

Guidelines for administering hydroxyurea in patients who develop sustained leukocytosis (>10 \(\times\) 10^9/l) after initiation of therapy are detailed below:

Hydroxyurea should be continued at a given dose to keep the WBC count <10 \(\times\) 10^9/l and subsequently tapered.

Recommendation for initiation of hydroxyurea:

<table>
<thead>
<tr>
<th>WBC 10 – 50 (\times) 10^9/l</th>
<th>500 mg four times a day</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC &gt; 50 (\times) 10^9/l</td>
<td>1000 mg four times a day</td>
</tr>
</tbody>
</table>

2.2 Treatment of coagulopathy

The pathogenesis of hemorrhagic complications of APL is complex and in particular includes factors of blood coagulation and fibrinolysis. The coagulopathy is biochemically conspicuous manifesting as a severe hypofibrinogenemia, increased levels of fibrin degradation products, a prolonged prothrombin time, a prolonged partial thromboplastin and thrombin time and thrombocytopenia.

It must be noted that the combination with ATRA can result in a reversion of the clotting disorder into a thrombophilic constellation with thromboembolic complications. Administration of fibrinogen (2 g i.v.) is recommended if fibrinogen levels are below 1 g/l. In case of unavailability of pure fibrinogen preparation, a substitution with fresh frozen plasma (FFP) is indicated. We recommend to keep platelet counts around 30-50 Gpt/l in the initial phase of therapy and Hb-values should be maintained at > 8 g/dl.

Treatment with tranexamic acid (antifibrinolytic agent such as cyklokapron® 3 x 1000 mg i.v. / d), fibrin-stabilizing factor (Factor XIII, e.g. Fibrogamin® 1250 E) and AT III (e.g. Cybernin® HS) at values below 50 % of normal range can be considered individually although not supported by randomized trials.\(^6^9\) The prophylactic administration of heparin has no proven benefit.
2.3 Differentiation syndrome (formerly “ATRA syndrome”)

During treatment with all-trans retinoic acid (ATRA) and ATO a differentiation syndrome can develop rapidly. It’s diagnosis should be clinically established by the presence of at least three of the following signs, but it is suspected already at presence of only one symptom:

- weight gain
- respiratory distress
- unexplained fever
- interstitial pulmonary infiltrates
- pleural or pericardial effusions with or without leukocytosis

No single sign or symptom may be considered per se as diagnostic for the syndrome. The release of cytokines leads to this syndrome, which can become fatal if untreated. Prophylaxis with prednisone is recommended.

In case of diagnosis of an APL differentiation syndrome the administration of APL therapy should be stopped in time. Early transfer of patients to an ICU for improved monitoring of vital signs should be considered. Immediate administration of dexamethasone (10 mg) i.v. every 12 hours for at least 3 days should be started at the first suspicion and a concomitant diuretic therapy are recommended until the disappearance of symptoms and signs. As soon as the patients’ clinical condition improve and the symptoms have disappeared and the WBC count is sustainably lowered to <10 x 10^9/l, the APL treatment with ATRA and/or ATO can be resumed at 50 % of the previous dose during the first 7 days. Thereafter in the absence of worsening of the previous toxicity, ATRA and/or ATO might be resumed at full dosage. In the case of the reappearance of symptoms, ATRA and ATO will be reduced at the previous dosage.

2.4 Pseudotumor cerebri with ATRA therapy

Particularly in younger patients a "pseudotumor cerebri" may occur during ATRA therapy, manifesting by headaches, nausea, vomiting and blurred vision. It is recommended to discontinue ATRA treatment temporarily and to administer opiates. As soon as the symptoms and the patients’ clinical conditions improve, the treatment with ATRA will be resumed at 50 % of the previous dose during the first 7 days after the amelioration of pseudotumor cerebri. Thereafter, in the absence of worsening of the previous toxicity, ATRA should be resumed at full dosage.

2.5 Hepatotoxicity with ATO/ATRA

Hepatotoxicity requires temporary suspension of ATRA and/or ATO. As soon as serum bilirubin and/or SGOT and/or alkaline phosphatase have been reduced to < 4 times the normal upper level, the treatment with ATRA and/or ATO will be resumed at 50 % of the
previous dose during the first 7 days. Thereafter, in the absence of worsening of the previous toxicity, ATRA and/or ATO should be resumed at full dosage.

### 2.6 QT prolongation with ATO therapy

Prolongation of the QT interval in the ECG has been observed during treatment with ATO. This can lead to ventricular tachycardia (torsade de pointes) with a fatal outcome. In this context, possible interaction with other drugs that prolong the QT interval must also be taken into account. For this reason, close monitoring of the ECG and of the electrolytes is necessary during treatment with ATO. In particular, the Mg++ and K+ levels should always be kept in the high-normal range, taking in consideration possible concomitant treatments that deplete electrolyte levels (e.g. amphotericin B, furosemide etc.). In ECG the QT interval is represented by the QRS complex, the ST segment and the T wave. Its measurement starts from the deepest point of Q wave to the end of T wave. This interval greatly depends on the heart rate and several formulas have been proposed to adjust the QT interval for heart rate in order to obtain the corrected QT interval (QTc); however, no one of these proposed formulas is satisfactory. Despite that, data from medical literature indicate that one of the most simple method for adjusting the QT interval for heart rate is the Fridericia formula:

\[
\text{QTc} = \frac{\text{QT}}{\sqrt[3]{\text{RR}}}
\]

For increased accuracy, the QT interval should be measured on serial ECGs and several successive beats and averaged for each ECG. The averaged QT value obtained should be used in the above formula in which all measurement must be expressed in msec (i.e.: 0,470 sec=470msec). Applying this formula, a QTc interval > 500 msec must be considered prolonged (both genders).

ATO should be discontinued together with any medication known to prolong the QTc interval and electrolytes should be repleted. The time between discontinuing ATO and normalization of the QTc interval may be several days. Once QTc is normalized, resume ATO at 0.075 mg/Kg (50%) for the first 7 days, and then if no further prolongation occurs, resume at 0.11 mg/Kg for a second week. Thereafter, if no prolongation occurs, resume ATO at full dose.
3 EVALUATION OF RESPONSE

For the evaluation of treatment response the following hematological and molecular remission criteria are used as basis for the documentation sheet (CRF).

3.1 Hematological remission criteria

**Hematological complete remission (CR)**
- < 5 % blasts without atypical promyelocytes in the bone marrow
- Neutrophils ≥ 1,0 Gpt/l
- platelets ≥ 100 Gpt/l

**Hematological incomplete remission (CRi)**
- < 5 % blasts without atypical promyelocytes in the bone marrow
- Neutrophils < 1,0 Gpt/l
- platelets < 100 Gpt/l

**Non-Response**
- ≥ 5 % blasts and atypical promyelocytes up to 60 days after beginning of induction therapy

**Hematological Relapse**
After a pre-existing documented morphological CR there is a relapse if:
- 0.1 Gpt/l of blasts in the peripheral blood
- percentage of blasts / atypical promyelocytes > 10 % in the bone marrow at any time during follow-up
- meningeosis leucomica
- bioptic verifiable extramedullary relapse

3.2 Molecular remission criteria

**Molecular Complete Remission (CRm)**
- absence of the PML-RARα hybrid transcript by RT-PCR in bone marrow samples

**Molecular Resistant Disease (RDm)**
- persistence of PML-RARα hybrid transcript in the bone marrow cells at the end of the last consolidation cycle
- it should be always confirmed in two consecutive bone marrow samples taken 2 weeks apart
**Molecular relapse**

- conversion from RT-PCR negative to positive PML-RARα hybrid transcript in the bone marrow samples collected at any time after the 3\textsuperscript{rd} consolidation cycle or
- recurrent PML-RARαPCR-positivity of two successive bone marrow samples in distance of 2-4 weeks after the last consolidation therapy
- conversion/ relapse should be always confirmed in two consecutive bone marrow samples taken 2 weeks apart

**4 DIAGNOSTIC EXAMINATION PROGRAM**

The general diagnosis of APL is based on the local standards. Close monitoring of the following lab parameters should be carried out especially during induction therapy: Quick, PTT, fibrinogen, hemoglobin, leukocytes, neutrophils, platelets, ATIII, factor XIII and D-dimers (depending on the severity of the bleeding disorders up to three times daily).

An ECG, echocardiographic examination (ejection fraction and valve abnormalities) is recommended before each induction therapy and after completion of treatment.

**Diagnostic examination schedule**

Molecular analyses (PCR) and morphological analyses of the bone marrow and peripheral blood are recommended

- at initial diagnosis
- after induction
- prior to the second and following consolidation therapy
- after the last consolidation therapy
- quarterly during maintenance therapy
- after therapy quarterly during a 5 year follow-up from the start of therapy
- suspicion of relapse

Cytogenetic and immunophenotype analyses should be performed at the initial diagnosis and in suspicion of relapse.

For patients with a relapsed APL an equal sample collection is also recommended.

A detailed diagnostic examination schedule is below-mentioned.
## Diagnosis or suspicion of relapse during induction

### Physical examination
- * (incl. comorbidities)
- Daily, including body weight
- Day 28/prior cons. 1
- Prior cons. 2
- Prior cons. 3
- Prior cons. 4 (if appropr.)
- After last cons.
- Maintenance (if appropr.)
- Follow-up (1st - 5th year)

### Blood Counts (1)
- Daily during 1st week, afterwards 3 x/week
- Day 28/prior cons. 1
- Prior cons. 2
- Prior cons. 3
- Prior cons. 4 (if appropr.)
- After last cons.
- Maintenance (if appropr.)
- Follow-up (1st - 5th year)

### BM for morphology
- *(6)*
- Day 28/prior cons. 1
- Prior cons. 2
- Prior cons. 3
- Prior cons. 4 (if appropr.)
- After last cons.
- Maintenance (if appropr.)
- Follow-up (1st - 5th year)

### BM for molecular biology (2)
- *(6)*
- Day 28/prior cons. 1
- Prior cons. 2
- Prior cons. 3
- Prior cons. 4 (if appropr.)
- After last cons.
- Maintenance (if appropr.)
- Follow-up (1st - 5th year)

### BM for cytogenetics
- *
- Day 28/prior cons. 1
- Prior cons. 2
- Prior cons. 3
- Prior cons. 4 (if appropr.)
- After last cons.
- Maintenance (if appropr.)
- Follow-up (1st - 5th year)

### BM for immunophenotyping (3)
- *
- Day 28/prior cons. 1
- Prior cons. 2
- Prior cons. 3
- Prior cons. 4 (if appropr.)
- After last cons.
- Maintenance (if appropr.)
- Follow-up (1st - 5th year)

### Coagulation tests (4)
- Daily until normalization, 2 x a week thereafter
- Day 28/prior cons. 1
- Prior cons. 2
- Prior cons. 3
- Prior cons. 4 (if appropr.)
- After last cons.
- Maintenance (if appropr.)
- Follow-up (1st - 5th year)

### Serum biochemistry (5)
- 2-3 x/ week during the first 3 weeks, then weekly until CR
- Day 28/prior cons. 1
- Prior cons. 2
- Prior cons. 3
- Prior cons. 4 (if appropr.)
- After last cons.
- Maintenance (if appropr.)
- Follow-up (1st - 5th year)
<table>
<thead>
<tr>
<th>Procedure</th>
<th>during induction</th>
<th>day 28/ prior cons. 1</th>
<th>prior cons. 2</th>
<th>prior cons. 3</th>
<th>prior cons. 4 (if appropr.)</th>
<th>after last cons.</th>
<th>maintenance (if appropr.)</th>
<th>Follow-up (1st - 5th year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiogram</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>once a year</td>
<td>once a year</td>
</tr>
<tr>
<td>Echocardiography (7)</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>once a year</td>
<td>once a year</td>
</tr>
<tr>
<td>Urine analysis</td>
<td>*</td>
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<tr>
<td>Hepatitis- and HIV-serology</td>
<td>*</td>
<td></td>
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<td></td>
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<tr>
<td>ChestX-ray</td>
<td>*</td>
<td></td>
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<td></td>
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<tr>
<td>Pregnancy test (if appropriate)</td>
<td>*</td>
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<td></td>
</tr>
</tbody>
</table>

(1) haemoglobin, leukocytes, platelets, neutrophils, blasts
(2) PML-RARA incl. isoforms, FLT3-ITD, FLT3-TKD
(3) HLA-DR, CD2, CD7, CD9, CD11b, CD13, CD14, CD15, CD19, CD33, CD34, CD56, CD117
(4) Quick, aPTT, fibrinogen, factor XIII, AT III, and D-dimers
(5) glucose, creatinine, uric acid, bilirubin, transaminases, alkaline phosphatase, LDH, sodium, potassium, calcium, phosphorus, magnesium, total proteins, albumin, cholesterol and triglycerides
(6) if not evaluable, repeat bone marrow on a serial basis until achievement of CR or failure
(7) incl. L-VEF

**Figure 3: Diagnostic examination recommendation**
5 LITERATURE


Further Literature

Link, H. Akute Promyelozytenleukämie: APL; M3-Leukämie. ONKODIN 2008
http://www.onkodin.de/zms/content/e2/e51675/e53188/e54107/index_ger.html

Lengfelder, E.; Platzbecker, U.; Niederwieser, D.; Schlenk, R. F.; Wörmann, B.
Leitlinie Akute Promyelozyten Leukämie, Dokumentenstand Februar 2012
http://www.dgho-onkopedia.de/de/onkopedia/leitlinien/akute-promyelozytaere-leukaemie

European PROMYSE registry for relapsed APL
http://www.leukemia-net.org/content/leukemias/aml/apl/apl_recommendations/index_eng.html