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Characteristics and outcome of patients with therapy-related acute promyelocytic leukemia front-line treated with or without arsenic trioxide

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AUTHOR CONTRIBUTIONS

SK and UP were responsible for the concept of this paper, contributed to the literature search data collection, analyzed and interpreted data, and wrote the manuscript. AB, JK and RFS analyzed and interpreted data and critically revised the manuscript. DG performed research. CT performed research and critically revised the manuscript. MAE, KN, PG, RKH, MRB, ZR, JM, JN, PZ, TS, NHR, RBW, EHE, JW, MG, AK, BDS, AKB, CR, ADH, GE, MT and MJL contributed patients and critically revised the manuscript. All authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST

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Abstract

Therapy-related acute promyelocytic leukemia (t-APL) is relatively rare, with limited data on outcome after treatment with arsenic trioxide (ATO) compared to standard intensive chemotherapy (CTX). We evaluated 103 adult t-APL patients undergoing treatment with all-trans retinoic acid (ATRA) alone (n = 7) or in combination with ATO (n = 24), CTX (n = 53), or both (n = 19). Complete remissions were achieved after induction therapy in 57% with ATRA, 100% with ATO/ATRA, 78% with CTX/ATRA, and 95% with CTX/ATO/ATRA. Early death rates were 43% for ATRA, 0% for ATO/ATRA, 12% for CTX/ATRA and 5% for CTX/ATO/ATRA. Three patients relapsed, two developed therapy-related acute myeloid leukemia and 13 died in remission including seven patients with recurrence of the prior malignancy. Median follow-up for survival was 3.7 years. None of the patients treated with ATRA alone survived beyond one year. Event-free survival was significantly higher after ATO-based therapy (95%, 95% CI, 82–99%) as compared to CTX/ATRA (78%, 95% CI, 64–87%; P= 0.042), if deaths due to recurrence of the prior malignancy were censored. The estimated 2-year overall survival in intensively treated patients was 88% (95% CI, 80–93%) without difference according to treatment (P= 0.47). ATO when added to ATRA or CTX/ATRA is feasible and leads to better outcomes as compared to CTX/ATRA in t-APL.

INTRODUCTION

Reports of patients with therapy-related acute promyelocytic leukemia (t-APL) as a result of previous exposure to chemotherapy and/or radiation have increased in recent years, particularly for those who received treatment with topoisomerase-II (topo-II) inhibitors or alkylating agents.¹⁻⁴ In recent publications, 15–21% of all APL cases were considered therapy-related,^{5,6} as compared to 8% reported in 2002.⁷ Prior malignancies most frequently include cancers of the breast and the genitourinary system, while non-malignant disorders, such as multiple sclerosis, may also be treated with cytotoxic chemotherapies.¹⁻⁴ The latency period between diagnosis of the primary disease and occurrence of t-APL ranges between a few months to several years, and may depend on the cumulative dose, dose intensity and type of preceding chemo and/or radiation therapy.¹⁻⁸

Nevertheless, the term ‘therapy-related’ leukemia is merely descriptive and based upon a patient’s history of exposure to chemo and/or radiotherapy. Whether the risk of developing therapy-related leukemia in general is increased due to an inherited susceptibility to develop neoplasia or due to the previous exposure to chemotherapy and/or radiation is currently not clear.⁹⁻¹¹ However, recent work has identified specific hot spots in the breakpoint region of PML and RARA genes as preferential sites of topo-II-mediated DNA damage, underscoring their causative role in the etiology of t-APL.^{4,12,13}

Since its clinical introduction in 1986, treatment with all-trans retinoic acid (ATRA) has significantly changed therapeutic success in APL.¹⁴ ATRA causes differentiation of abnormal promyelocytes to mature granulocytes.¹⁵ However, although complete remissions (CR) were achieved with single-agent ATRA in up to 80–90% patients with newly diagnosed and relapsed APL, remissions were typically not sustained.^{14,16-20}

These findings led to the concurrent use of ATRA with chemotherapy (either an anthracycline plus cytarabine or an anthracycline alone) as the standard of care for induction in newly diagnosed APL.²¹ More recently, the combination of arsenic trioxide (ATO) with ATRA have been shown to be a very effective chemotherapy-free treatment strategy in de novo APL, with a CR rate of 96%.²² In addition, published data of a large multicenter phase 3 randomized trial on the direct comparison of ATO/ATRA vs ATRA in combination with idarubicin (AIDA) or mitoxantrone in the Gruppo Italiano Malattie EM atologiche dell’Adulto (GIMEMA)/Programa para el Estudio de la Terapéutica en Hemopatías Malignas (PETHEMA) scheme showed very promising results in favor of ATO/ATRA, with a 2-year event-free survival (EFS) of 97 vs 86% ($P=0.02$).²³ Within this trial, early mortality as well as hematological toxicities were significantly lower in patients treated with ATO/ATRA as compared to AIDA.²³ Additional support comes from another publication out of the Medical Research Council with a 4-year EFS of 91% after ATO/ATRA as compared to 70% after chemotherapy (CTX)/ATRA ($P=0.002$).²⁴ Therefore, this non-chemotherapeutic approach seems to be of great benefit.

Prior publications have suggested that characteristics and outcomes of t-APL when treated appropriately were similar to those of de novo APL patients,^{5,7} but this has not been systematically evaluated in a large cohort of patients. Most importantly, the clinical impact

of ATO/ATRA on outcome in patients with t-APL is unknown, and this was the rationale for this multi-institutional analysis.

PATIENTS AND METHODS

Patients and treatment

Information on 103 patients with t-APL occurring after chemotherapy and/or radiation for a previous neoplasm or non-malignant disorder between 1991 and 2015 was collected from 11 study groups/institutions in the US and Europe. Patients with APL that occurred after a neoplasm treated by surgery or hormonal therapy only were excluded. To obtain patient information, detailed case report forms (including type of primary malignancy or non-malignant disorder and related treatment, occurrence of t-APL, its baseline characteristics, t-APL treatment, adverse events during t-APL treatment, response as well as follow-up data) were sent to all participating centers.

Diagnosis of APL was based on French-American-British Cooperative Group criteria,²⁵ and, after 2003, on revised International Working Group criteria.²⁶ Chromosome banding was performed using standard techniques, and karyotypes were described according to the International System for Human Cytogenetic Nomenclature.²⁷ The diagnosis was confirmed by either reverse-transcriptase polymerase chain reaction or fluorescence in situ hybridization detection of the PML-RARA fusion gene in bone marrow by standard methods. FLT3 mutation screening for internal tandem duplications (ITD) and point mutations within the tyrosine kinase domain (TKD) was carried out as previously described.^{28,29} Data collection and analysis were approved by the Institutional Review Boards.

Treatment

Fifty-three (51.5%) t-APL patients were treated with ATRA and an anthracycline (daunorubicin or idarubicin) as induction and different chemotherapies in combination with ATRA as consolidation therapy according to treatment protocols active in various countries. These protocols included the AIDA 2000 protocol of the Italian GIMEMA study group,³⁰ the PETHEMA LPA99 and LPA2005 protocols^{31,32} and the United Kingdom AML15³³ and AML17²⁴ protocols. Twenty-four (23.3%) patients were treated with ATO/ATRA (according to Lo-Coco et al.²³ (n = 21) or Burnett et al.²⁴ (n = 3)) and 19 (18.4%) patients received ATO/ATRA in combination with chemotherapy (according to Gore et al.³⁴ or comparable schemes). Seven (6.8%) patients with advanced age and/or poor performance status received monotherapy with ATRA only.

Response was assessed according to Cheson et al.²⁶

Statistical analyses

Survival endpoints including overall survival (OS), EFS, relapse-free survival (RFS), cumulative incidence of relapse and cumulative incidence of death in CR were defined as recommended.²⁶ In addition to the international criteria we included death due to primary malignancy as an event for EFS and RFS.

Comparisons of patient characteristics were performed with the Kruskal–Wallis rank sum test for continuous variables and Fisher’s exact test for categorical variables, respectively. A multivariable linear regression model was used to identify factors that influence the duration of the latency period from prior malignancy/non-malignant disorder to the diagnosis of t-APL measured on log-scale, including the covariates age at diagnosis of primary malignancy/non-malignant disorder, gender, prior chemotherapy and prior radiation. The chemotherapeutic subcategories ‘prior treatment with intercalating agents’ or ‘topo-II inhibitors’ were not included due to low numbers.

The median follow-up time was computed using the reverse Kaplan–Meier estimate.³⁵ The Kaplan–Meier method was used to estimate the distribution of RFS, EFS and OS.³⁶ Confidence interval (CI) estimation for survival curves was based on the cumulative hazard function using Greenwood’s formula for variance estimation. Log-rank tests were employed to compare survival curves between groups. A Cox proportional hazards regression model was used to identify prognostic variables for EFS, RFS and OS.³⁷ The following variables were included in the Cox models: age at diagnosis of t-APL, gender, t-APL treatment (ATO/ATRA vs CTX/ATO/ATRA vs CTX/ATRA), prior chemotherapy, prior radiotherapy, white blood cells (WBC; dichotomized according to high vs intermediate/low risk) and duration of the latency period between diagnosis of primary malignancy/non-malignant disorder and the occurrence of t-APL. All statistical analyses were performed with the statistical software environment R, version 3.3.1, using the R packages prodlm, version 1.5.7 and survival, version 2.39–5.³⁸

RESULTS

In total, 103 adult t-APL patients, diagnosed between 1991 and 2015 from 11 study centers/institutions in the US and Europe, were included. Median age was 59 years (range, 18–80 years). Most of the patients had French-American-British M3 (n = 94), whereas the M3 variant was very rare (n = 7); information on sub-variant category was missing in n = 2 patients.

Risk categorization based on WBC at diagnosis was available in 99 (96%) of the 103 patients and was low/intermediate-risk (WBC < 10.0 G/l) in 79 (80%) and high-risk (WBC ≥ 10.0 G/l) in 20 (20%) patients.

Information on cytogenetics was available in 84 (82%) patients. In 62 (74%) of the 84 patients, the balanced t(15;17) translocation was the sole abnormality, whereas in 22 (26%) patients, the translocation was accompanied by additional cytogenetic abnormalities, most frequently various deletions (n = 8) including del(7q) (n = 2) and del(5q) (n = 1), followed by variant translocations (n = 7) as well as trisomy 8 (n = 5) or trisomy 8 in combination with other abnormalities (n = 1; del(9)(q21) and monosomy X). One patient had an additional trisomy 21.

Regarding FLT3-ITD and TKD mutations, information was available in 51 (50%) of the 103 patients. Of those, 17 (33%) patients had FLT3-ITD, three (6%) had a FLT3-TKD mutation and three (6%) additional patients displayed both FLT3-ITD and TKD mutation. Notably,

FLT3-ITD mutated patients had significantly higher WBC at diagnosis as compared to FLT3 wild type patients ($P = 0.03$).

Congruently, cytogenetic as well as molecular data on FLT3 were available in 44 patients. Interestingly, only 4 of 15 (27%) patients with additional cytogenetic abnormalities were FLT3 mutated (two with an ITD, one with a TKD and one additional patient with both mutations). In contrast, 18 of 29 (62%) patients without additional cytogenetic abnormalities displayed FLT3 mutations ($P = 0.05$).

Information on the PML-RARA transcript isoform (breakpoint cluster region, BCR) was available in 52 patients for BCR3 (short isoform) and 45 patients for BCR1 (long isoform). Of those, 58% ($n = 30/52$) displayed the BCR3 isoform, whereas 33% ($n = 15/45$) were BCR1-positive.

Primary diseases, previous therapy and latency period to the occurrence of t-APL

The median latency period between diagnosis of primary malignancy/non-malignant disease and the occurrence of t-APL was 3.5 years (range, 0.4–26.2 years). Eighty-seven (84%) patients with t-APL had a previous solid cancer (Table 1). Among these, breast cancer was the most common neoplasm ($n = 38$; 37%), followed by prostate ($n = 14$; 14%), head and neck ($n = 9$; 9%) and gastrointestinal ($n = 9$; 9%) cancers. Five (5%) patients (one male/four females) had two solid cancers prior to the occurrence of t-APL (colon and prostate; breast and lung; cervix and breast; breast and uterus; ovarian and breast; $n = 1$ each). Eight (8%) patients had a primary hematologic malignancy: five with non-Hodgkin lymphoma and three with Hodgkin lymphoma. In addition, eight (8%) patients had undergone cytotoxic therapy for the treatment of an autoimmune disease (four with multiple sclerosis treated with mitoxantrone, four with rheumatologic disorders treated with methotrexate; Table 1).

Treatment prior to the occurrence of t-APL included chemotherapy only in 28 (27%) patients, radiation in 40 (39%), and both chemotherapy and radiation in 35 (34%), respectively. Detailed information on type of chemotherapeutic agents was available in 53 (84%) of the 63 patients, who had been treated with chemotherapy with or without radiation (Table 2). Of those, only 16 (30%) patients received single-agent chemotherapy. For further analysis, we classified chemotherapeutic agents according to mechanism of action.⁸ In univariable analysis, prior treatment with neither intercalating agents ($P = 0.81$) nor topo-II inhibitors ($P = 0.46$) was associated with the length of the latency period between diagnosis of primary malignancy and the occurrence of t-APL. In multivariable analysis, only younger age at diagnosis of primary malignancy ($P = 0.07$) and prior radiation ($P = 0.06$) were in trend associated with a shorter latency period.

Comparison of baseline characteristics

Women were more frequently affected than men (binominal test, $P < 0.001$), possibly due to the high frequency of t-APL after treatment of breast cancer. In a direct comparison of the four treatment groups (CTX/ATRA; ATO/ATRA; CTX/ATO/ATRA; ATRA), the baseline characteristics were comparable except for age ($P = 0.002$) and platelet counts ($P = 0.009$), in that patients treated with ATRA alone were older and had lower platelet counts (Table 3).

Response to induction therapy

Response data were available in 100/103 (97%) patients (missing: CTX/ATRA, $n = 2$; ATO/ATRA, $n = 1$). Early death (ED) rates were 43% for ATRA ($n = 3$), 0% for ATO/ATRA, 12% for CTX/ATRA ($n = 6$) and 5% for CTX/ATO/ATRA ($n = 1$). Of those, $n = 5$ EDs occurred between 1991–2009 (after $n = 52/103$ (50%) patients had been included) and additionally $n = 5$ EDs between 2010–2015.

CRs were achieved after induction therapy in 57% of the patients treated with ATRA ($n = 4$), 100% with ATO/ATRA ($n = 23$), 78% with CTX/ATRA ($n = 40/51$) and 95% with CTX/ATO/ATRA ($n = 18$). Five of the CTX/ATRA patients achieved a partial remission after induction therapy. All of them went on to consolidation therapy and achieved CR thereafter (Table 4).

Survival analysis

Median follow-up for survival was 3.7 years. The estimated 2-year EFS, RFS and OS rates in intensively treated patients (excluding the patients treated with ATRA only) were 84% (95% CI, 75–90%), 84% (95% CI, 75–91%) and 88% (95% CI, 80–93%), respectively and were not significantly different according to treatment groups ($P = 0.23$, $P = 0.24$ and $P = 0.47$, respectively).

Stratified by treatment, estimated 2-year EFS rates were 78% (95% CI, 64–87%) in patients treated with CTX/ATRA, 89% (95% CI, 64–97%) in the ATO/ATRA group and 95% (95% CI, 68–99%) in the CTX/ATO/ATRA group (Figure 1a). The estimated 2-year RFS rates were 78% (95% CI, 64–87%) in the CTX/ATRA group, 90% (95% CI, 68–98%) in the ATO/ATRA and 95% (95% CI, 68–99%) in the CTX/ATO/ATRA groups. The estimated 2-year OS rates for patients receiving CTX/ATRA were 84% (95% CI, 71–92%), 89% (95% CI, 64–97%) for ATO/ATRA and 95% (95% CI, 68–99%) for CTX/ATO/ATRA (Figure 1b). None of the patients treated with ATRA alone survived beyond 1 year. Cumulative incidence of relapse including relapse and occurrence of secondary AML as events in intensively treated patients showed a strong trend towards a higher cumulative incidence of relapse after treatment with CTX/ATRA as compared to ATO-based regimens (including ATO/ATRA and CTX/ATO/ATRA; $P = 0.07$), whereas cumulative incidence of death was not different between the two treatment groups ($P = 0.33$).

In an additional sensitivity analysis we censored patients with death from recurrent primary malignancy at the date of death for EFS. The estimated 2-year modified-EFS rate in this analysis was significantly higher in patients treated with ATO-based therapy, including ATO/ATRA and CTX/ATO/ATRA (95%, 95% CI, 82–99%) as compared to those patients treated with CTX/ATRA (78%, 95% CI, 64–87%; $P = 0.042$, Figure 2).

In multivariable analysis, neither prior therapy with CTX, nor prior radiation, nor length of latency period from prior malignancy were associated with EFS ($P = 0.88$, $P = 0.34$, $P = 0.92$, respectively), RFS ($P = 0.85$, $P = 0.35$, $P = 0.88$, respectively) or OS ($P = 0.77$, $P = 0.69$, $P = 0.88$, respectively). Furthermore, we were interested in the outcome of t-APL patients according to risk categorization (high vs low WBC). In univariable analyses, neither EFS ($P = 0.57$), RFS ($P = 0.63$), nor OS ($P = 0.79$) according to initial WBC were different.

Three patients relapsed after 9, 12 and 18 months, all after CTX/ATRA treatment. In one of these patients, relapse was detected at the MRD level before frank hematological relapse, leading to administration of pre-emptive salvage therapy. All of the relapsed APL patients were successfully salvaged with ATO/ATRA $\pm$ CTX and went on to autologous (n = 1) or allogeneic transplant (n = 2). Two patients developed therapy-related acute myeloid leukemia (t-AML) with a complex karyotype after 47 and 74 months. Again, both t-AMLs occurred after CTX/ATRA treatment. Both patients were refractory to salvage CTX and died shortly thereafter.

Thirteen patients died in APL remission due to relapse of the prior malignancy (CTX/ATRA, n = 2; ATO/ATRA, n = 1; CTX/ATO/ATRA, n = 1; ATRA, n = 3), infections (CTX/ATRA, n = 2 and ATO/ATRA, n = 1), development of diffuse large B-cell lymphoma (CTX/ATRA, n = 1), cardiopulmonary arrest during treatment (ATO/ATRA, n = 1) and unknown reason (CTX/ATRA, n = 1).

Regarding toxicity during induction therapy patients who received CTX/ATRA or CTX/ATO/ATRA were categorized into one group, since ATO within the latter treatment scheme was given during consolidation therapy only.³⁴ Febrile neutropenia of grade 3 during induction therapy was less frequent in patients treated with ATO/ATRA as compared to CTX/ATRA or CTX/ATO/ATRA (P= 0.03, Table 5), whereas the occurrence of other grade 3 toxicities was not different between treatment groups.

DISCUSSION

Therapy-related APL is increasing in prevalence with longer life expectancy and improved survival of patients treated with chemotherapy and/or radiation for prior malignancies and other disorders.^{2,5,7,39} However, there is a paucity of prospective treatment data since these patients have often been excluded from clinical trials. In our retrospective analysis of a large cohort of 103 t-APL patients, spanning a time-period of almost 25 years, more than two thirds of the patients were diagnosed after 2006. The median latency period between diagnosis of primary malignancy and occurrence of t-APL was 3.5 years, which is in line with published data.^{5,39} Consistent with data obtained in t-AML,⁸ t-APL patients in our series were older at diagnosis compared to what has been reported in de novo APL,^{5,7,39} possibly reflecting the longer life span required to develop two or more malignancies, as well as a prolonged risk exposure. In addition, we found a high proportion of female patients (68% were female; P < 0.001),^{2,7} which may be related to the widespread use of anthracycline-based chemotherapy for breast cancers. As previously published for t-AML,⁸ younger age at diagnosis of primary malignancy was associated with a shorter latency period to the occurrence of t-APL. However, there was no association between treatment with anthracyclines or topo-II inhibitors and a short latency period for the development of t-APL.⁸

T-APL occurred after treatment of multiple sclerosis with mitoxantrone therapy in only a small number of our patients, but all of them were female, again explaining the higher frequency of female gender in t-APL, as compared to what has been reported in de novo AML. In contrast to Beaumont et al.,² who reported a high frequency of 18% of lymphomas

prior to the occurrence of t-APL, we did not observe this phenomenon. Our series included five patients who had two primary malignancies prior to the diagnosis of t-APL. Three of them were treated with CTX/ATRA, one with ATO/ATRA and one with ATRA only. The latter one died due to the underlying primary malignancy after 10 months and one patient treated with CTX/ATRA developed a diffuse large B-cell lymphoma after 16 years. The other patients were still alive after follow-up times of 7 months, 3.5 years and 9.8 years.

Previous studies in t-APL patients reported an incidence of additional abnormalities ranging from 25 to 36%,^{2,39} with an even higher incidence of 45% published recently in a single-institution report.⁴⁰ Although we could not confirm this high incidence of additional abnormalities, the incidence of 26% observed in our cohort is in line with previously published data.^{2,39} Besides variant translocations and deletions, the most frequently recurring mutation was trisomy 8, again in agreement with published studies.^{2,40} Concurrent FLT3-ITD mutations were present in 39% and were significantly associated with high WBC at diagnosis,^{41–43} which has also been described in de novo APL.⁴⁴ To date, there are still conflicting data regarding the impact of additional chromosomal or genetic aberrations on outcome in APL patients.^{41–51} In our large cohort, neither the presence of additional cytogenetic abnormalities ($P = 0.43$) nor a concurrent FLT3-ITD ($P = 0.79$) had an impact on OS, which is in line with published data.^{43,45–47}

Regarding the BCR isoform, we did not observe a higher frequency of the BCR1 isoform in our t-APL patients, and virtually none of our BCR1-positive patients had received prior treatment with topo-II inhibitors, which is in contrast to the data reported by Ottone et al.⁵¹ One explanation for the observed discrepancies might be related to substantial differences in the patients analysed. Our study included only a low number of patients with t-APL arising after multiple sclerosis, whereas the majority of the t-APL patients published by Ottone et al.⁵¹ had multiple sclerosis as their underlying disease, implicating heterogeneous treatments and therefore induction of potentially distinct pathogenetic pathways. Nevertheless, both the predominance of the short BCR3 isoform in t-APL⁵ and the comparable frequency of FLT3-ITD mutations in our cohort to what has been described for de novo APL are in concordance with findings reported by others.^{5,52} Although there might be a higher susceptibility towards leukemogenesis in t-APL patients, these results suggest a similar composition of de novo as compared to t-APL.^{51,53}

In contrast to published data in de novo APL, high WBC had no impact on outcome.⁴⁴ Nevertheless, our series included only a low number of high-risk patients; thus, no firm conclusion can be drawn regarding this issue.

Most of the available studies reported outcome after chemotherapy and ATRA for t-APL patients,^{2,6,7,39} whereas data on outcome after ATO/ATRA are scarce.⁴⁰ In our large cohort of 103 t-APL patients, those who had been treated with ATO-based therapy had a higher CR rate and a lower ED rate as compared to patients treated with CTX/ATRA. The higher induction mortality in patients treated with CTX/ATRA may reflect the cumulative effect of prior chemotherapies and additional t-APL chemotherapy toxicities. General supportive care seemed not to have a major impact on outcome in the years covered in our report, since the

ED rate was almost stable over different time-periods. However, due to low numbers of events, we could not include the year of treatment in multivariable analysis.

If death due to recurrence of the primary malignancy was included as an event, EFS, RFS and OS were not significantly different between patients treated with ATO-based therapy as compared to CTX/ATRA. However, if these events were censored at the time point of death, EFS in ATO-based therapy was significantly higher as compared to CTX/ATRA and rates of EFS were very similar to what was achieved in de novo APL.²³ This indicates a similar responsiveness to therapy of t-APL as compared to de novo APL, thereby suggesting similar pathogenesis.

With a median follow-up of 3.7 years, none of the patients treated with ATO-based therapy have relapsed so far, whereas three patients treated with CTX/ATRA relapsed and two patients developed t-AML with a complex karyotype. Again, both t-AMLs occurred after CTX/ATRA treatment. Of note, all of the t-APL relapses could be successfully salvaged with ATO/ATRA ± CTX and went on to autologous (n = 1) or allogeneic (n = 2) transplant. The absence of secondary therapy-related myeloid neoplasms in patients treated with ATO-based regimens represents a potential major improvement in the treatment of a disease in which high cure rates are achieved. After a median RFS of 0.7 years (range, 0–16 years), 13 patients experienced other late adverse events, most frequently recurrence of the underlying primary malignancy or infections, whereas t-APL was still in remission.

Regarding toxicities during induction therapy, severe febrile neutropenia was significantly less frequent after ATO/ATRA as compared to CTX/ATRA or CTX/ATO/ATRA treatment, again indicating a beneficial effect of the CTX-free approach. Nevertheless, due to the retrospective nature and since adverse events had not been documented in all patients, no firm conclusions can be drawn regarding this issue.

Since the CTX-free regimen with ATO/ATRA has been proven to be highly effective in de novo APL and has become standard first-line therapy in non-high-risk de novo APL, it seems to be prudent to expand this approach to t-APL.^{54,55}

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Figure 1.
Kaplan–Meier plots on EFS (a) and OS (b) in intensively treated patients with t-APL.

Figure 2. EFS according to treatment in intensively treated patients (excluding therapy with ATRA only) with t-APL. Death due to the primary malignancy (n = 4) has been censored at the time point of death.

Table 1

Primary diseases in patients with t-APL

Primary diseases	Numbers of patients	%
Solid cancers	87	84
Cancers of females		
Breast ^a	35	34.0
Cervix ^a	4	3.9
Uterus ^a	6	5.8
Ovary ^a	2	1.9
Cancers of males		
Prostate ^a	14	13.6
Testis	2	1.9
Cerebral cancers		
Pituitary adenoma	1	1.0
Head and neck cancers		
Thyroid	5	4.9
Larynx	1	1.0
Hypopharynx	1	1.0
Parotid	1	1.0
Brachial cleft	1	1.0
Thoracic cancers		
Lung ^a	3	2.9
Abdominal cancers		
Esophagus	1	1.0
Pancreatic	1	1.0
Colon/rectum ^a	7	6.8
Soft tissue tumors		
Liposarcoma	2	1.9
Hematologic malignancies	8	7.8
Non-Hodgkin lymphoma	5	4.9
Hodgkin lymphoma	3	2.9
Autoimmune diseases	8	7.8
Multiple sclerosis	4	3.9
Rheumatologic	4	3.9

Abbreviation: t-APL, therapy-related acute promyelocytic leukemia.

^aFive patients had two solid tumors prior to the occurrence of t-APL (breast and uterus, n = 1; cervix and breast, n = 1; breast and lung, n = 1; ovarian and breast, n = 1; colon/rectum and prostate, n = 1). Therefore, the total number of malignancies/non-malignant disorders does not add up to 103.

Table 2

Therapy of primary malignancy/non-malignant disorder prior to the occurrence of t-APL

Treatment ^a	Number of patients N= 103	%
Chemotherapy	N= 63	
CTX alone	28	44
combined with RT	35	56
Missing	–	–
Chemotherapy	N= 63	
Alkylating agents	39	62
Topo-II inhibitors	3	5
Antimetabolites	19	30
Antitubulins	16	25
Intercalating agents	31	49
Missing	12	19
RT only	40	39
Missing	–	–

Abbreviations: ATO, arsenic trioxide; ATRA, all-trans retinoic acid; CTX, chemotherapy; RT, radiotherapy; t-APL, therapy-related acute promyelocytic leukemia; Topo-II, topoisomerase-II inhibitors. Percentages may not add to 100 due to rounding.

^aNo difference according to treatment groups (CTX/ATRA; ATO/ATRA; CTX/ATO/ATRA; ATRA only) of patients with t-APL.

Comparison of presenting clinical and laboratory findings according to the applied therapy of patients with t-APL

Table 3

Characteristics	CTX/ATRA n = 53	ATO/ATRA n = 24	CTX/ATO/ATRA n = 19	ATRA only n = 7	P-value
Age, years					
Median	57.0	60.0	56.0	69.6	0.002
Range	19.6–80.0	24.0–79.1	18.0–79.0	64.0–73.0	
Gender, no. (%)					
Male	13 (25)	6 (25)	10 (53)	4 (57)	0.5
Female	40 (75)	18 (75)	9 (47)	3 (43)	
WBC, $\times 10^9/l$					
Median	1.9	1.9	1.6	4.5	0.86
Range	0.3–145	0.3–57.2	0.2–126	0.6–75.1	
Missing	4	1	–	–	
Hemoglobin, g/dl					
Median	10.1	9.3	9.7	9.3	0.88
Range	4.9–13.8	3.8–13.2	6.8–13.5	8.4–13.5	
Missing	3	1	–	–	
Platelet count, $\times 10^9/l$					
Median	36	34	24	11	0.009
Range	12–220	12–121	9–103	3–72	
Missing	4	1	–	–	
Percentage of PB blasts					
Median	2	35	6	35	0.16
Range	0–94	0–81	0–86	2–76	
Missing	25	10	2	1	
Percentage of BM blasts					
Median	70	80	72	80	0.87
Range	2–95	0–94	8–95	79–90	
Missing	19	3	1	3	
LDH value, U/l					
Median	274	303	255	387	0.48

Characteristics	CTX/ATRA n = 53	ATO/ATRA n = 24	CTX/ATO/ATRA n = 19	ATRA only n = 7	P-value
Range	124–1654	147–1112	139–2320	262–675	
Missing	23	5	2	0	
Risk categorization ^a no. (%)					
Low/Intermediate	39 (80)	21 (88)	15 (79)	5 (71)	0.63
High	10 (20)	3 (12)	4 (21)	2 (29)	
Missing (no.)	4	–	–	–	
Cytogenetics, no. (%)					
t(15;17) sole	34 (77)	12 (57)	13 (87)	3 (75)	0.20
t(15;17) & additional abn	10 (23)	9 (43)	2 (13)	1 (25)	
Missing (No.)	9	3	4	3	
FLT3-ITD, no. (%)					
Mutated	7 (26)	6 (43)	5 (71)	2 (66)	0.10
Unmutated	20 (74)	8 (57)	2 (29)	1 (33)	
Missing (no.)	26	10	12	4	
FAB, no. (%)					
M3	49 (94)	20 (87)	19 (100)	6 (86)	0.23
M3 variant	3 (6)	3 (13)	–	1 (14)	
Missing (no.)	1	1	–	–	
Extramedullary disease no. (%)					
Yes	–	23 (100)	17 (90)	7 (100)	0.12
No	40 (100)	–	2 (10)	–	
Missing (no.)	13	1	–	–	

Abbreviations: abn, abnormality; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; BM, bone marrow; CTX, chemotherapy; FAB, French-American-British; ITD, internal tandem duplication; LDH, serum lactate dehydrogenase; No, number; PB, peripheral blood; t-APL, therapy-related acute promyelocytic leukemia; WBC, white blood counts.

^aRisk categorization based on WBC at diagnosis (low/intermediate-risk: WBC < 10.0 G/l; high-risk: WBC ≥ 10.0 G/l). Percentages may not add to 100 because of rounding.

Table 4

Response to induction therapy according to treatment strategy

	CTX/ATRA % (No.)	ATO/ATRA % (No.)	CTX/ATO/ATRA % (No.)	ATRA only % (No.)
CR	78 (40)	100 (23)	95 (18)	57 (4)
PR	10 (5)	–	–	–
ED	12 (6)	–	5 (1)	43 (3)

Abbreviations: ATO, arsenic trioxide; ATRA, all-trans retinoic acid; CR, complete remission; CTX, chemotherapy; ED, early death; No, numbers; PR, partial remission.

Table 5

Grade 3 and higher toxicities according to treatment strategy during induction therapy

	CTX/ATRA & CTX/ATO/ATRA ^a no. (%)	ATO/ATRA no. (%)	P-value
Febrile neutropenia	23/34 (68)	3/11 (27)	0.03
Hematological adverse events ^b	32/34 (94)	9/11 (82)	0.25
^c Other adverse events	30/41 (73)	11/15 (73)	1.00

Abbreviations: ATO, arsenic trioxide; ATRA, all-trans retinoic acid; CTX, chemotherapy; No, numbers. Denominators are not consistent with the total number of patients of the respective treatment group due to missing values.

^aPatients who received CTX/ATRA or CTX/ATO/ATRA were categorized into one group since ATO in the latter group was given during consolidation therapy only.³⁴

^bAnemia and/or thrombopenia and/or neutropenia.

^cOther adverse events: adverse events excluding anemia, thrombopenia or neutropenia. Toxicities were classified according to CTCAE v. 4.0.