Therapy-Related Acute Promyelocytic Leukemia

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Abbreviations

AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
ATO	Arsenic trioxide
ATRA	All-trans retinoic acid (tretinoin)
CR	Complete remission
DNMT3A	DNA methyltransferase 3A
FLT3	FMS-like tyrosine kinase-3 receptor
GIMEMA	Gruppo Italiano Malattie EMatologiche dell'Adulto
IDH1/2	Isocitrate dehydrogenase 1 and 2
LCH	Langerhans cell histiocytosis
MDS	Myelodysplastic syndrome
MS	Multiple sclerosis
OS	Overall survival
PML	Promyelocytic leukemia
RARA	Retinoic acid receptor alpha
RT	Radiation therapy
t-APL	Therapy-related acute promyelocytic leukemia
TET2	Tet oncogene family member 2 isocitrate
t-MN	Therapy-related myeloid neoplasm

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Introduction

Exposure to DNA-damaging agents, either by certain cytotoxic drugs or by radiation therapy, has been shown to predispose to later development of myeloid malignancies including myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), and acute myeloid leukemia (AML), which together constitute the World Health Organization category of therapy-related myeloid neoplasms (t-MN) [1]. t-MN currently accounts for about 10–20% of AML and MDS cases and exhibits characteristic chromosomal abnormalities and latency periods as well as poor prognoses in most cases [2]. t-MN after exposure to alkylating agents or radiation typically develops 5–7 years after initial therapy and is most often associated with a complex karyotype or abnormalities of chromosomes 5 or 7. There is often an antecedent myelodysplastic phase [3, 4]. t-MN after exposure to topoisomerase II inhibitors develops more quickly, generally within 1–3 years, and often involves rearrangements at chromosome bands11q23 or 21q22 [5, 6].

Less commonly, t-MN will present with a t(15;17)(q22;q21) and clinical features of acute promyelocytic leukemia (APL). These cases of therapy-related acute promyelocytic leukemia (t-APL) most commonly arise after exposure to topoisomerase II inhibitors but have also been observed after alkylating agents, antimitotic agents, and radiation therapy. t-APL represents a

distinct subset of t-MN with clinical features, treatment options, and prognosis similar to those now seen in de novo APL.

Several rich sources of clinical information on t-APL are available in the literature and will be discussed throughout this chapter (see Table 19.1). In the largest series of t-APL cases to date, Beaumont et al. examined in detail 106 cases of t-APL diagnosed at 45 medical centers in three European countries between 1982 and 2001 [7]. In the same article, that group reviewed 77 pooled case reports from the literature up to that point [8]. In 2000, the International Workshop on the relationship of prior therapy to balanced chromosome aberrations in therapy-related myelodysplastic syndromes and acute leukemia was held in Chicago and described 511 cases of t-MNs, including 41 cases of t-APL [9]. In addition, Pulsoni et al. reported on the Italian cooperative group Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) experience between 1984 and 1998 comparing 51

cases of t-APL to 641 cases of de novo APL [10]. Together, these reports help form the basis of clinical knowledge of t-APL.

Epidemiology

t-APL is an uncommon disease that accounts for a small proportion of all APL and t-MN cases. Earlier studies in particular highlighted the infrequency of t-APL diagnoses. Detourmignies et al. examined 284 cases of APL that were diagnosed between 1982 and 1991 at 7 European medical centers and found that only 16 cases (5.6%) were related to prior cytotoxic therapy [8]. Among the GIMEMA APL cohort, t-APL accounted for 4.8% of the 51 cases studied [10]. Kantarjian et al. reported on 112 patients with t-MNs seen at the MD Anderson Cancer Center between 1973 and 1985 and found that only two cases (1.8%) had a t(15;17) [11]. Among 63 patients with t-MNs seen at the University of Chicago prior to 1985, 2 (3%) had a t(15;17) and clinical characteristics of

Table 19.1 Key t-APL case series

Series	Number of patients	Primary diagnosis	Exposure	Latency, months	Outcomes
French, Spanish, and Belgian report [7]	106	Breast cancer 60% Non-Hodgkin lymphoma 15% Hodgkin lymphoma 2% Other solid tumors 23% Nonmalignant disorders 2%	Combined chemotherapy and RT 46% Chemotherapy alone 28% RT alone 26%	25 (range, 4–276)	Those in pre-ATRA era (n = 14), CR 87% In ATRA era, CR 80% 8-year OS 59%
Literature review [7, 8]	77	Breast cancer 17% Non-Hodgkin lymphoma 5% Hodgkin lymphoma 16% Other solid tumors 31% Nonmalignant disorders 29%	Not reported	25	Not reported
International Workshop [9]	41	Breast cancer 44% Non-Hodgkin lymphoma 17% Hodgkin lymphoma 10% Other solid tumors 27% Nonmalignant conditions 2%	Combined chemotherapy and RT 54% Chemotherapy alone 17% RT alone 21%	29 (range, 9–175)	CR 74% Number in continuous CR at 5 years 57%
GIMEMA [10]	51	Breast cancer 29% Non-Hodgkin lymphoma 18% Hodgkin lymphoma 6% Other solid tumors 47%	Combined chemotherapy and RT 20% Chemotherapy alone 20% RT alone 33% Surgery alone 27%	36 (range, 8–366)	CR 97% 4-year OS 84%

APL [12]. The 2000 International Workshop in Chicago identified 8% of t-MN with balanced chromosome aberrations as t-APL [9].

While still rare, the incidence of t-APL appears to be on the rise although this may be the result of greater recognition for this striking disease. Beaumont et al. reported on 106 patients with t-APL diagnosed between 1982 and 2001 in France, Spain, and Belgium and found that 26 of those patients were diagnosed with t-APL in the first 10-year period, compared to 80 who were diagnosed in the second 10-year period [7]. Other centers have noted an apparent increase in the number of cases of t-APL as well, even after retrospectively examining all prior APL diagnoses to determine whether prior cytotoxic exposure had been overlooked and the therapy-related cases had been misclassified in earlier years. At the University Hospital of Lille, France, the proportion of APL cases that occurred after prior cytotoxic therapy rose considerably from 5% in the 1984–1993 period to 22% between 1994 and 2000 [7, 13]. A similar trend was noted at the MD Anderson Cancer Center, where 2% of all APL cases were therapy-related in 1986, compared to 12% in 1996 [11, 14]. Therefore, there may be a true increase in the incidence of t-APL as opposed to increased recognition of t-APL as an entity. This rise largely parallels the rising incidence of t-MN overall over the past few decades and may reflect increased use of specific leukemogenic therapies as well as improved survivorship from primary malignancies [15, 16].

Disease Presentation

Clinical Features

In general, clinical characteristics seen in t-APL parallel those of de novo APL. t-APL is seen across all adult age groups, with median age at diagnosis between 49 and 57 years [7–10]. Hematologic parameters are comparable between therapy-related and de novo groups [7, 9, 10]. Female predominance of t-APL has been demonstrated in multiple studies, most likely reflecting the frequency of topoisomerase II inhibitor use

and radiation therapy for the treatment of breast and gynecologic malignancies [7, 9, 10, 14]. This differs from de novo APL, which exhibits no predisposition by sex. The GIMEMA group noted several other differences in those with t-APL compared to de novo disease in their study [10]. They found that those with t-APL presented with a worse performance status ($P < 0.005$) and older age ($P < 0.05$). Those with therapy-related disease also had higher fibrinogen levels and few hemorrhagic complications than their de novo counterparts. Elliott et al. found a slightly lower BMI in patients with therapy-related disease, but other clinical features were similar [17]. Overall, these few small differences in clinical features do not translate to differences in clinical outcome, as will be discussed below.

Pathologic Features

Pathologic features of t-APL, including cytologic, cytogenetic, and molecular abnormalities, have been shown to be similar to those seen in de novo APL. Duffield et al. compared bone marrow specimen from nine patients with t-APL to those with de novo disease and found no differences in morphology or immunophenotype between the two groups [18]. In contrast to non-promyelocytic t-MN where an antecedent myelodysplastic phase is common, cases of t-APL lack such a phase and present with overt leukemia [7, 19].

In addition to t(15;17), other chromosomal abnormalities occasionally occur in APL. The incidence and types of additional abnormalities found in t-APL are similar to those also seen in de novo APL. While the prognostic impact of additional chromosomal abnormalities in APL has been a matter of debate in the past, in the current era of therapy, they do not seem to confer adverse risk [20–23]. Overall in APL, 26–33% of cases harbor additional chromosomal abnormalities, the most common being trisomy 8 (12%), followed by abnormalities in chromosomes 9 (2%), 7 (2%), 21 (2%), and 17 (1%) [20]. Beaumont et al. reported a similar incidence of additional chromosomal abnormalities in t-APL, with a slightly different distribution. Within this

group, trisomy 8 was seen in only 5% of cases, and the remaining abnormalities predominantly involved chromosomes 5, 7, or 17 [7]. Among the 41 cases analyzed through the International Workshop, 41% of cases included additional abnormalities, most frequently trisomy 8 in 12%. There was no association between additional chromosomal abnormalities and either age or type of previous therapy in this series. While occasional variant translocations involving RARA that confer resistance to standard therapy have been reported in de novo APL, they are rare, and such cytogenetic variants have not been reported in t-APL.

Molecular profiling has been reported for a small number of patients with t-APL. FMS-like tyrosine kinase-3 receptor (*FLT3*) gene mutations are commonly seen in de novo APL. However, they do not appear to connote the same negative prognosis that is seen in non-promyelocytic AML. Several groups have compared the frequency of *FLT3* mutations between therapy-related and de novo APL cases and reported somewhat discordant results. Yin et al. found a high incidence of *FLT3* mutations (42% of 12 t-APL cases studied) [24]. Ottone et al. found a similar incidence, 30% in t-APL compared to 44% in de novo APL ($P = 0.50$) [25]. Duffield et al. found that all five t-APL cases studied had a *FLT3* mutation compared to 59% of de novo cases ($P = 0.41$) [18]. This variation may be due to the small numbers in each series and to differences in the patient population studied. One study focused on patients with prior malignancies, while another focused on patients with multiple sclerosis (MS). Ottone et al. also tested for mutations in several other genes associated with myeloid malignancies, including tet oncogene family member 2 (*TET2*), isocitrate dehydrogenases 1 and 2 (*IDH1* and *IDH2*), and DNA methyltransferase 3A (*DNMT3A*) [25]. They found a *DNMT3A* pathogenic mutation in one t-APL case but none in the de novo APL group. They reported one *IDH1* mutation in a de novo case. *TET2* polymorphisms were common in both groups. Further evaluation with larger cohort sizes and more extensive mutation panels will clarify the mutational profiles of these two disorders.

Prior Diagnosis and Exposures

t-APL has been reported following a variety of therapies used for several different malignant and nonmalignant disorders (see Table 19.2). The most commonly implicated antecedent therapies are topoisomerase II-targeting agents such as mitoxantrone, etoposide, and anthracyclines (particularly epirubicin) [7, 9, 10]. The mechanism by which topoisomerase II inhibitors initiate development of t-APL has been described in detail by Grimwade and colleagues and will be discussed below (see Pathogenesis). However, t-APL has also been described after treatment with other DNA-damaging therapies such as alkylating agents, antimetabolites, external beam radiation, and radioactive iodine. The leukemogenic risk may be dose-dependent for some agents such as etoposide, but not for others such as mitoxantrone [26–28]. While t-APL typically develops rapidly with a median latency of 25–32 months, cases have been reported as early as 4 months after first exposure and as late as 276 months after therapy [7, 9, 28, 29]. Thus, the latency period, both at

Table 19.2 Risk factors for the development of t-APL

t-APL risk factors
Primary diagnosis
Malignant
Breast cancer
Non-Hodgkin lymphoma
Hodgkin lymphoma
Uterine cancer
Testicular cancer
Other solid tumors
Nonmalignant
Multiple sclerosis
Psoriasis
Langerhans cell histiocytosis
Exposures
Topoisomerase II inhibitors
Mitoxantrone
Etoposide
Anthracyclines
Bimolane
Radiation therapy
External beam radiation
Radioactive iodine

median and the range, is similar to what is observed in cases of non-promyelocytic t-MN that develops after topoisomerase II inhibitors.

The majority of t-APL cases have arisen after treatment for solid malignancies. In the Beaumont series of 106 t-APL cases, the most common primary disorder was breast cancer (60%) followed by non-Hodgkin lymphoma (15%), Hodgkin lymphoma (2%), uterine cancer (4%), lung cancer (1%), other solid tumors (19%), and, rarely, nonmalignant disorders (2%). Treatments for these primary tumors included chemotherapy alone (28%), radiation alone (26%), or both (46%). Most patients received an alkylating agent or a topoisomerase II inhibitor, in 64% and 57%, respectively [7]. Findings were similar in the 41 patients included in the International Workshop, where breast cancer was again the most common primary diagnosis (44%), followed by non-Hodgkin lymphoma (17%), Hodgkin lymphoma (10%), other solid tumors (27%), and nonmalignant conditions (2%). Most had received both chemotherapy and radiation (54%), though in this series, fewer received chemotherapy alone (17%) and more received radiation alone (29%) [9].

While the largest series of t-APL cases have primarily identified those that develop after treatment of primary cancers, the literature is ripe with smaller series and case reports describing t-APL after treatment for nonmalignant disorders. Multiple reports describe an association between APL and psoriasis, particularly after treatment with the antimitotic drugs, bimolane and razoxane. Both of these drugs function through inhibition of topoisomerase II and were previously used in China to treat both neoplastic disorders and psoriasis [30, 31]. Ge et al. reported on 17 cases of APL in patients with psoriasis diagnosed over 10 years at the First Affiliated Hospital at Harbin Medical University, China [32]. These cases represented 8.3% of all APL diagnoses at that center during that time period. Only four patients had received prior therapy with bimolane, suggesting that there could be additional risk conferred by the underlying psoriasis itself. Another report by Wang et al. examined 100 cases of acute leukemia that developed in patients with psoriasis [33]. In their series, APL was by far the most common

leukemia subtype, present in 53 of the cases. Of those, 40% had been treated with bimolane or related analogues, 42% had been treated with agents other than bimolane, and 18% had not been treated. Various theories have been proposed to explain the increased leukemia susceptibility among patients with psoriasis even in the absence of treatment, including antigenic stimulation, and the presence of chromosomal fragile sites [34, 35]. Interestingly, downregulation of the retinoic acid receptor alpha (RARA) in the epidermis leads to abnormal keratinocyte proliferation that is responsive to retinoic acid therapy, suggesting some biologic similarity between APL and psoriasis. These authors speculate that additional predisposition to APL may exist in these psoriasis patients even prior to DNA-damaging agents [36, 37].

Children treated for Langerhans cell histiocytosis (LCH) with etoposide have also been found to have increased risk for t-APL. In an analysis of 77 case reports of t-APL, 12 of those cases were found to have occurred in children with LCH. All 12 had been treated with etoposide, and 9 of the 12 had received cumulative doses >4500 mg/m^2 [7, 26, 27]. However, in another series of 348 patients with LCH treated at several European medical centers with etoposide, no cases of t-APL were reported. In this series, all patients received total etoposide doses of <2000 mg/m^2, suggesting a dose-dependent leukemogenic effect of this agent [26].

Similarly, patients with multiple sclerosis (MS) treated with the topoisomerase II inhibitor mitoxantrone have developed t-APL. Ammatuna et al. reported on 33 patients at various European medical centers who had MS and were subsequently diagnosed with t-APL [28]. Among those patients, 30/33 had received mitoxantrone. Their median cumulative dose of mitoxantrone was 112 mg and ranged from only 14 mg in one patient up to 242 mg, suggesting an idiosyncratic relationship and the lack of a dose-response risk in this situation. The three patients who had not received mitoxantrone had been treated with steroids alone, interferon beta with sequential steroids, and interferon beta plus azathioprine. Many additional case reports of t-APL after mitoxantrone for MS can be

found in the literature [38–46]. Other leukemogenic risk factors may be present in some patients with MS, such as genetic variants involving DNA repair (*BRCA2* and *XRCC5*) that could predispose to translocation events or variants affecting the metabolism of chemotherapeutics (such as *CYP3A4*) that could result in increased cellular exposure to drugs such as mitoxantrone [47].

Several cases of APL after immunosuppressive treatment alone for nonmalignant conditions have been reported, but it is controversial whether these cases should be considered therapy-related. In Japanese centers, two children developed APL after receiving living donor partial orthotopic liver transplantation. The first was 12 years old and received a liver transplant for ornithine transcarbamylase deficiency, followed by tacrolimus and azathioprine immunosuppression posttransplant. Azathioprine has been associated with t-MN after solid organ transplantation [48]. The second, a 4-year-old girl, received a liver transplant for congenital biliary atresia and received tacrolimus after transplant. APL developed after latencies of 21 months and 46 months, respectively. Both were treated with all-trans retinoic acid (ATRA, tretinoin) and chemotherapy, and both attained complete remissions (CR), which were ongoing at the time of publication [49]. One case of APL in a patient with Crohn's disease treated with the anti-TNF alpha monoclonal antibody infliximab has been reported in the literature [50]. It would be difficult to infer causality from this single case report alone. Treatment with TNF antagonists and the presence of inflammatory bowel disease have both been associated with increased risk of developing lymphoid neoplasms, but a causal link to myeloid neoplasms remains unclear [51–54].

Pathogenesis

In virtually all cases of APL, a balanced translocation between the long arms of chromosomes 15 and 17 results in juxtaposition of the promyelocytic leukemia (*PML*) gene with the retinoic acid receptor alpha (*RARA*) gene [55, 56]. The resulting *PML-RARA* fusion protein functions as an aberrant retinoid receptor that resists physiologic retinoid-induced differentiation of myeloid cells [57]. In

cases of de novo APL, the inciting factors that lead to this translocation event are largely unknown. In contrast, in t-APL, the molecular mechanisms underlying the cleavage of DNA strands and subsequent translocation are well described. This is particularly true after treatment with topoisomerase II inhibitors, which represents the most common setting for development of t-APL.

Topoisomerases are enzymes that regulate the DNA topology through the introduction of single- or double-stranded DNA breaks at specific breakpoints. In the case of topoisomerase II, the enzyme generates transient double-stranded breaks through the formation of a covalent cleavage complex, thus allowing for modulation of DNA supercoiling and release of knots or tangles. DNA repair mechanisms subsequently religate the cleaved DNA strands. Modern pharmacology has been successful in exploiting these mechanisms for therapeutic purposes, and today topoisomerase II is a crucial target for a number of chemotherapeutic agents. Chemotherapeutics that affect topoisomerase II can be divided into two categories. The first includes compounds that decrease the overall activity of the enzyme, such as anthracyclines (i.e., epirubicin, daunorubicin, and doxorubicin). The second group increases transition levels of the topoisomerase II-DNA cleavage complexes, leading to inhibition of cell replication and transcription. Drugs in this category are referred to as topoisomerase II poisons and include etoposide and mitoxantrone [58, 59].

The association between myeloid neoplasms and topoisomerase II-damaging agents has been recognized for quite some time, but only more recently have the molecular mechanisms underlying this relationship come to light. Mistry et al. examined differences in the genomic breakpoint regions between three groups of patients: those with t-APL that developed after exposure to mitoxantrone, those with t-APL that developed after other exposures (e.g., radiation therapy or epirubicin), and those with de novo APL [60]. They found that the breakpoints in cases of t-APL arising after mitoxantrone treatment were clustered in an eight base pair region in intron 6 within the *PML* gene. This breakpoint region corresponded to a site that was preferentially cleaved by mitoxantrone at nine times the frequency that was seen in the absence of the drug. While breakpoints in *RARA* were more

dispersed, they similarly corresponded to preferential sites of DNA cleavage by mitoxantrone. Short, homologous sequences in *PML* and *RARA* were observed, suggesting that DNA repair occurred by nonhomologous end joining. One of their patients had only received 15 mg of mitoxantrone, supporting previous observations for an absence of dose-response effect with mitoxantrone. A subsequent series of 12 patients with t-APL that developed after treatment with mitoxantrone for MS demonstrated that the *PML* breakpoint fell within the previously identified breakage "hotspot" in 42% of cases [41]. An extension of this study included 23 patients with t-APL and demonstrated DNA breakpoints within the *PML* "hotspot" in 39% of t-APL cases overall, compared to none of the de novo cases ($P = 0.007$) [61]. In addition, breakpoints in *RARA* were found to cluster in a region of intron 2 in 65% of t-APL cases compared to 28% of de novo cases.

Patients who developed t-APL after treatment with epirubicin have also been found to share breakpoints that cluster within specific hotspots. Mays et al. examined genomic features in six patients who developed t-APL after treatment with epirubicin for breast cancer and observed specific breakpoint clustering within both *PML* and *RARA* loci [62]. Within *PML*, three of the six patients were found to have breakpoints in intron 6 that occurred at close approximation to one another, which was unlikely to occur by chance ($P = 0.014$). These intron 6 breakpoints occurred outside of the hotspot region that had previously been identified for mitoxantrone-induced APL cases. Other *PML* breakpoints were found in intron 3 and exon 7. The *RARA* breakpoints occurred within intron 2 in all six cases. In two of those cases, the breakpoints occurred within four nucleotides of each other, which was unlikely to occur by chance ($P = 0.017$). In all cases, the breakpoints in both chromosomes were found to occur at preferential sites for epirubicin-induced DNA cleavage by topoisomerase II.

From these observations, models have been generated by Grimwade and coworkers to depict the formation of the leukemogenic balanced translocation of chromosomes 15 and 17 after exposure to a topoisomerase II inhibitor (see Fig. 19.1) [62]. In this model, topoisomerase II
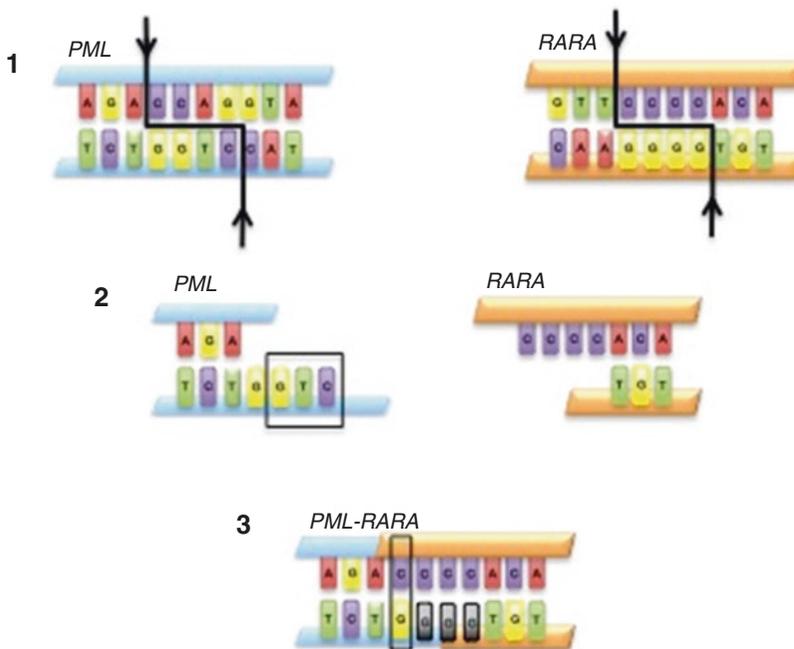
Fig. 19.1 Model for the mechanism of *PML-RARA* translocation in topoisomerase II inhibitor-induced t-APL. (*1*) Topoisomerase II induces 4-bp nicks in double-stranded DNA at preferential sites within *PML* and *RARA* genes. (*2*) Exonucleases digest bases from 5′ overhang (indicated by *black box*). (*3*) Nonhomologous end joining occurs (indicated by *black box*), followed by template-directed DNA polymerization (indicated by *gray text*) and strand ligation, resulting in the formation of a *PML-RARA* fusion gene (Reproduced with permission) [62]

induces 4 base pair nicks in double-stranded DNA at preferential sites within *PML* and *RARA* genes on chromosomes 15 and 17, respectively, and on other genes. Exonucleolytic processing occurs, followed by nonhomologous end joining. Gaps are filled by template-directed DNA polymerization and mismatch repair mechanisms, and strands are ligated. If this results in translocation between chromosomes 15 and 17, the *PML-RARA* fusion gene may be generated. The discovery of susceptible breakage sites and creation of this model for translocation formation have illuminated the likely molecular mechanisms for t-APL development and perhaps represent a step toward discovering mechanisms for the pathogenesis of de novo APL.

Treatment Approaches

While most t-MN confer a significantly worse prognosis compared to their cytogenetically matched de novo counterparts, those with APL seem to do similarly well regardless of whether the disease is related to prior cytotoxic therapy [2, 7, 10, 63, 64]. A report from the GIMEMA retrospectively identified 51 patients with APL after a prior cancer diagnosis and compared the outcomes of these patients to those with de novo APL [10]. The majority of t-APL patients (31 out of 51) were treated with a standard regimen of ATRA plus idarubicin. Despite older age and worse performance status among the t-APL patients in this series, outcomes were equally good between the two groups. CR rates were 97% and 93% in the t-APL group and de novo APL group, respectively, and 4-year overall survival (OS) was 85% and 78%, respectively. Other case series similarly show encouraging long-term survival for patients with t-APL treated with ATRA plus chemotherapy [7, 9, 65].

In the era of arsenic trioxide (ATO) therapy, these favorable and comparable outcomes between de novo and t-APL have held up. Dayyani et al. conducted a retrospective analysis of 29 patients with t-APL treated at the MD Anderson Cancer Center and compared outcomes of patients treated with ATRA/ATO ($n = 19$) to those treated with ATRA/anthracycline-based chemotherapy ($n = 10$) [66]. Remission rates were similar between the two groups, with CRs in 89% and 70%, respectively ($P = 0.35$). Median OS was not reached at last follow-up for the ATRA/ATO group, compared to 161 weeks for the ATRA/chemotherapy group ($P = 0.79$). Similarly, Ge et al. examined 17 patients with psoriasis-associated t-APL treated with ATO-based induction and post-remission therapy and reported an 88% CR rate and estimated a 3-year OS rate of 77% ± 12% [32]. Given this overall favorable response profile, patients with t-APL should be treated according to conventional APL treatment algorithms, and one can expect favorable outcomes quite similar to those with de novo disease. In contrast to other t-MN, intensification of therapy based on therapy-related status, such as inclusion of allogeneic stem cell transplantation, is typically not necessary in t-APL to achieve cure.

Although primary chemotherapy resistance is common in other t-MN subtypes, drug resistance is rare in t-APL. In de novo APL, acquired mutations in *PML* or *RARA* have been shown to confer resistance to ATRA or ATO infrequently [67–71]. One such case of ATO resistance in a patient with t-APL has been analyzed and reported on by Iaccarino et al. [72]. The patient was found to have a point mutation in *PML* in both the rearranged and unrearranged alleles, as well as two mutations in the rearranged *RARA* gene, none of which were present prior to ATO treatment. Madan et al. characterized the molecular signature of relapsed APL and found that mutations in *PML* or *RARA* were commonly acquired at the time of relapse [73]. Further study is needed to determine whether patients with APL may benefit from screening for these or similar mutations to identify those at risk for developing relapse or resistance.

Future Directions

While much has been learned about t-APL over the past 15 years, additional questions remain. Further clarification is needed regarding the apparent rise in incidence of t-APL in recent years.

Preventive strategies such as minimizing exposure to topoisomerase II inhibitors and radiation therapy whenever possible may be helpful in mitigating this upturn. Whether adjunctive therapy with hematopoietic growth factors such as filgrastim facilitates the leukemogenic effects of intensive chemotherapy remains to be determined. Further evaluation of screening strategies for early detection of t-APL in the most high-risk situations, prior to the development of complications such as bleeding, is also warranted. A genetic predisposition to t-APL may exist in a proportion of patients, as is the case in other t-MNs; however, this requires further investigation [74]. In addition, molecular characterization of t-APL by high-throughput methods may identify those at higher risk for drug resistance or relapse. Lastly, models for the pathogenesis of t-APL may help elucidate mechanisms of de novo disease development.

Conclusions

Treatment with certain agents, particularly topoisomerase II inhibitors, can result in DNA damage within specific hotspots that predispose to development of balanced translocations in chromosomes 15 and 17. Radiation therapy is also implicated in these chromosomal rearrangements. t-APL is associated with a short latency period and typically develops within 2–3 years after the causative exposure. While the breakpoints in t-APL differ from those found in de novo APL, the phenotype that results is largely identical. Clinical and pathologic features of t-APL closely reflect those of de novo disease. Outcomes are similar to de novo APL, and same treatment algorithms should be employed.

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