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Incidence of secondary neoplasms in patients with acute promyelocytic leukemia treated with all-*trans* retinoic acid plus chemotherapy or with all-*trans* retinoic acid plus arsenic trioxide

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Abstract

The incidence and pattern of secondary neoplasms in patients with acute promyelocytic leukemia (APL) treated with ATRA-containing regimens is not well-described. We compared secondary neoplasms in 160 patients with APL treated with ATRA plus idarubicin (n=54), or ATRA plus arsenic trioxide (ATO) (n=106) for the incidence of secondary cancers per unit time of follow-up. Median follow-up times for the two cohorts were 136 and 29 months, respectively. Nine patients developed secondary cancers in the chemotherapy group. These included two breast cancers, three myelodysplastic syndromes/acute myeloid leukemia, one vulvar cancer, one prostate cancer, one colon cancer and one soft tissue sarcoma. A melanoma and one pancreatic cancer developed in the ATO group. We conclude that treatment of patients with APL using the non-chemotherapy regimen of ATRA plus ATO is not associated with a higher incidence of secondary cancers (p=0.29) adjusted for unit time of exposure.

Keywords

Secondary Neoplasm; Arsenic; Promyelocytic; Leukemia

Introduction

Acute promyelocytic leukemia (APL), a subtype of acute myeloid leukemia (AML), is now considered curable. The incidence of this subtype of AML is higher in younger patients occurring from the second decade of life, and declining after the age of 60.(1) In the United States, approximately 600–800 new cases are diagnosed per year.(2) The cytogenetics of this subtype of AML are well known with t(15:17) (q22;q12) leading to the PML-RARA

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Disclosure

The authors report no disclosures.

transcript occurring in the majority of cases. APL comprises 5% of all AML cases in the United States.(2)

Despite a high rate of early mortality in untreated APL patients, occurring mostly due to complications such as disseminated intravascular coagulation, APL patients achieve longer survival rates with the implementation of all-*trans* retinoic acid (ATRA)-containing regimens. Studies have shown that concomitant administration of ATRA and chemotherapy at induction improves disease-free survival and overall survival significantly.(3, 4)

The innovative combination of ATRA with arsenic trioxide (ATO) has had a remarkable effect on the management and outcome of APL, especially in older patients.(5–7) In one study, the 5-year overall survival rate for patients with APL treated with single-agent ATO as front-line therapy was 64.4%.(8)

APL survivors face the potential problem of developing secondary malignancies. A number of prior studies have found myeloid neoplasms and specifically therapy-related myelodysplastic syndrome (MDS) in patients who have been successfully treated for APL and have a long-term disease-free course.(9–14)

It is thought that secondary neoplasms may result from exposure to alkylating agents or DNA topoisomerase II inhibitors.(15, 16) Case reports of renal cell carcinoma and T-lymphoblastic lymphoma developing following successful treatment of APL have also been published.(17, 18)

In all of the above-mentioned reports, all the affected APL patients had been treated with a conventional combination of chemotherapy and ATRA. To date, there are no reports of secondary malignancies among patients with APL treated with intravenous ATO as a component of both the induction and consolidation therapy.

The goal of this study was to compare the incidence and pattern of secondary malignancies in patients with APL treated with two ATRA-containing regimens.

Patients and Methods

We searched the database of the Department of Leukemia at The University of Texas MD Anderson Cancer Center to identify patients with APL who were treated with ATRA-containing regimens at the institution between 1991 and 2009. We identified 187 patients with APL and retrospectively examined the medical records of these patients. Of the 187 patients, 27 (14%) had a history of prior unrelated cancer and were excluded from the study. Of the remaining 160 patients, 54 had been induced with ATRA plus chemotherapy (idarubicin based) and 106 patients received induction therapy with ATRA plus ATO. The induction regimens are detailed in Table 1.

The median age of the patients was 44 years (range 13–81), 28 patients were older than 60 years; 84 patients were female. Fifty patients were considered to have high-risk disease with white blood cell counts of more than $10 \times 10^9/L$ at the time of diagnosis. The characteristics

of the patients induced with either ATRA plus chemotherapy or ATRA plus ATO are shown in Table 2.

The diagnoses of secondary malignancies were confirmed with biopsy and cytopathologic evaluation. Complete response was defined as normalization of peripheral blood counts and bone marrow analysis. Overall survival rate was calculated by the Kaplan-Meier method and log-rank test. The probability of developing secondary malignancy was estimated by the cumulative incidence method, calculated from the date of complete response. The study was approved by the institutional review board and conducted in accordance with the Declaration of Helsinki.

Results

Among the 160 patients with APL in this study, we identified 11 patients who developed secondary malignancies. The median duration of follow-up time for the whole cohort was 55 months (range 1–193). Median duration of time from APL diagnosis to secondary malignancy diagnosis (latency period) was 59 months (range 16–125).

Among 11 patients with secondary malignancies, nine patients had been induced and consolidated by ATRA plus idarubicin and two patients had received ATRA plus ATO. Median latency periods for the two cohorts were 57 months (range 25–125) and 44 months (range 16–71), respectively. Among the patients treated with chemotherapy plus ATRA we found the following secondary malignancies: three patients with MDS, two patients with breast cancer, one patient with vulvar cancer, one patient with prostate cancer, one patient with colon cancer, and one patient with soft tissue sarcoma. Of the two patients who developed secondary malignancies after receiving ATRA plus ATO, one developed melanoma of the skin and the second one developed pancreatic cancer. The cumulative incidence of secondary malignancies in the two cohorts is shown in Figure 1.

Table 3 illustrates the characteristics of the patients who developed secondary malignancies after treatment with ATRA plus chemotherapy or ATRA plus ATO.

With a median follow-up duration of 55 months, 26 of the 160 patients in this study have died. Of note, six of the 26 (23%) who died had developed secondary malignancies. Figure 2 demonstrates the statistically significantly shorter survival among this group of patients.

Discussion

Advances in treating patients with APL have resulted in long-term survival leading to the possibility of emergence of late complications such as central nervous system relapse and secondary malignancies. The pathogenesis of therapy-related MDS/AML has been extensively studied. Pedersen-Bjergaard et al and others have detailed the chromosomal aberrations and gene mutations detected in therapy-related MDS/AML.(16) Recurring cytogenetic abnormalities such as loss of sections of the long arm or the entire chromosomes 5 or 7 (5q–/–5, 7q–/–7) are frequently observed in this setting. Among the 11 patients with secondary malignancies in our study, three patients had MDS with chromosome 5 and 7 abnormalities (2 del(7) and 1 del(5)). Both had received an anthracycline-based regimen for

induction and consolidation. To our knowledge, there are no prior reports of a direct causal association between anthracyclines and secondary solid cancers. However, prior studies of patients with Hodgkin's lymphoma have shown an increased overall risk for solid cancers in patients treated with chemotherapy and radiotherapy.(19–22)

In our study, only 2 of 106 (2%) patients in the ATRA plus ATO group developed secondary malignancies compared to 9 of 54 (17%) treated with prior chemotherapy, suggesting that the incidence of secondary malignancies is at least not increased using the former regimen. However, a major limitation of the study is that the follow-up time in the cohort treated with ATRA plus ATO was much shorter than follow-up for the ATRA plus chemotherapy group, given the fact that treatment with ATRA plus ATO is relatively new. Further follow-up from recently conducted prospective randomized trials are ideally required to confirm our observation.(23) Furthermore, detailed molecular may further insight into the mechanisms of pathogenesis of secondary cancers. In our study, cytogenetic and mutational analyses were not available for all patients at the time diagnosis of secondary tumors, especially in solid cancers.

In summary, the regimen of ATRA plus ATO in patients with APL is not inferior to regimens of ATRA plus chemotherapy in terms of acquiring secondary malignancies.

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Figure 1.
Estimated cumulative incidence curve for secondary malignancies in the two cohorts (ATRA plus chemotherapy vs. ATRA plus ATO) as competing events

Figure 2.
Kaplan-Meier survival curves showing shorter survival among APL patients with secondary malignancy vs. APL patients without secondary malignancy

Table 1

Drug doses and schedules in APL induction regimens

Drug	Dose	Schedule	Route
ATRA + ATO ± GO			
ATRA	(45 mg/m ²)	Starting on d 1, once daily	PO
ATO	(0.15 mg/kg)	Starting d 1 or d 10, once daily until CR	IV
GO	(9 mg/m ²)	d 1	IV
ATRA + idarubicin			
ATRA	(45 mg/m ²)	Starting d 1, once daily	PO
IDA	(12 mg/m ²)	d 1–4	IV

ATRA, all-*trans* retinoic acid; ATO, arsenic trioxide; GO, gemtuzumab ozogamicin; PO, orally; CR, complete remission; IV, intravenously.

GO was added to the regimen for patients with a white blood cell count >10,000/L.

Table 2

Patient characteristics.

Characteristic	ATRA + CT* (n = 54)	ATRA + ATO (n = 106)	p Value
Age			
Median age at Dx, years [range]	38 [13 – 67]	46 [14 – 81]	0.001
Age > 60 years, n (%)	2 (3.7)	26 (24.5)	0.001
Sex			
Women, n (%)	30 (55.6)	54 (50.9)	0.52
Risk category*			
Low risk, n (%)	34 (63.0)	76 (71.7)	0.3
High risk, n (%)	20 (37.0)	30 (28.3)	
Response			
CR, n (%)	51 (94.4)	105 (99.1)	
Follow-up			
Median follow-up time, months [range]	136 [5–193]	29 [1–93]	

CT, conventional chemotherapy; ATRA, *all-trans* retinoic acid; ATO, arsenic trioxide.

* High risk: white blood cell count $> 10 \times 10^9/\text{L}$ at the time of diagnosis.

Table 3

Characteristics of patients treated with ATRA plus chemotherapy and ATRA plus ATO

Secondary Cancer	Age	Sex	Risk	Res-ponse	Duration from APL to SM (months)	Cyto-Genetics
ATRA plus chemo						
Breast Ca	42	F	Low	CR	54	NA
Breast Ca	59	F	Low	CR	59	t (2;4)
Prostate Ca	60	M	Low	CR	118	Diploid
Vulvar Ca	20	F	Low	CR	125	NA
Colon Ca	63	M	High	CR	68	Diploid
Soft tissue sarcoma	20	F	High	CR	83	NA
MDS	26	F	High	CR	25	del 7
MDS	34	F	High	CR	36	del 5
MDS	46	F	Low	CR	36	del 7
ATRA plus ATO						
Melanoma	64	F	Low	CR	16	Diploid
Pancreatic CA	74	F	Low	CR	71	NA

ATRA, *all-trans* retinoic acid; ATO, arsenic trioxide; CR, complete remission; SM, secondary malignancy; Ca, cancer; F, female; MDS, myelodysplastic syndrome; M, male; NA, not available.