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Increased Incidence of Transformation and Myelodysplasia/Acute Leukemia in Patients With Waldenström Macroglobulinemia Treated With Nucleoside Analogs

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ABSTRACT

Purpose
Nucleoside analogs (NAs) are considered as appropriate agents in the treatment of Waldenström macroglobulinemia (WM), a lymphoplasmacytic lymphoma. Sporadic reports on increased incidence of transformation to high-grade non-Hodgkin's lymphoma and development of therapy-related myelodysplasia/acute leukemia (t-MDS/AML) among patients with WM treated with NAs prompted us to examine the incidence of such events in a large population of patients with WM.

Patients and Methods
We examined the incidence of these events in 439 patients with WM, 193 and 136 of whom were previously treated with and without an NA, respectively, and 110 of whom had similar long-term follow-up without treatment. The median follow-up for all patients was 5 years.

Results
Overall, 12 patients (6.2%) either developed transformation (n = 9; 4.7%) or developed t-MDS/AML (n = 3; 1.6%) among NA-treated patients, compared with one patient (0.4%) who developed transformation in the non-NA treated group ($P < .001$); no such events occurred among untreated patients. Transformation and t-MDS/AML occurred at a median of 5 years from onset of NA therapy. The median survival of NA-treated patients who developed transformation did not differ from other NA-treated patients as a result of effective salvage treatment used for transformed disease. However, all NA-treated patients who developed t-MDS/AML died at a median of 5 months.

Conclusion
These data demonstrate an increased incidence of disease transformation to high-grade NHL and the development of t-MDS/AML among patients with WM treated with NAs.

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INTRODUCTION

Waldenström macroglobulinemia (WM) is an indolent lymphoma characterized by accumulation of lymphoplasmacytic cells in the bone marrow (BM) and production of a monoclonal immunoglobulin M protein.[1] This condition is considered to be lymphoplasmacytic lymphoma as defined by the WHO classification system.[1,2] Nucleoside analogs (NAs), such as fludarabine and 2-chlorodeoxyadenosine (2-cda/cladribine), are considered as appropriate first-line agents for the treatment of WM.[1,2] Response rates range from 40% to 90% in the front-line and salvage settings.[1,2] The main complications of these agents are myelosuppression and immunosuppression, especially of T cells, leading to an increased risk of infections and a treatment-related mortality rate of up to 5% in some series.[2] In addition, stem-cell collection may also be problematic after prolonged exposure to NAs.[1]

Transformation to Richter syndrome is a well-known long-term complication in chronic lymphoid leukemia (CLL) and is considered as a natural evolution of CLL to an aggressive non-Hodgkin's lymphoma (NHL).[3] However, transformation events related to treatment have been reported in CLL and linked to extensive use of NA therapy.[4] Transformation events have been occasionally reported in WM, either without identified etiology[5,6] or after treatment with nucleoside analogs or chlorambucil.[7-10]

An increased incidence of therapy-related myelodysplastic syndrome/acute myeloid leukemia (t-MDS/AML) has also been reported with the use of chemotherapeutic agents, such as anthracyclines and alkylating agents in NHL.[11] A higher than expected incidence (1.2%) of t-MDS/AML has also been reported in patients with CLL after treatment with fludarabine and chlorambucil.[12] A few small studies have also reported sporadic incidence of t-MDS/AML among patients with WM after NA treatment, ranging from 3% to 7%.[8,9,13]

We therefore sought to delineate the incidence of transformation and t-MDS/AML in a large population of patients with WM and to determine the potential relationship between these events and treatment with NAs.

PATIENTS AND METHODS

Patients

We retrospectively studied 439 consecutive patients with the consensus panel definition of WM observed at our institution.[14] Among these patients, 329 were treated with (n = 193; NA group) or without (n = 136; non-NA group) an NA, and 110 patients remained untreated. The study was approved by the Dana-Farber Cancer Institute institutional review board.

Statistical Analysis

The distribution of demographic and baseline laboratory data is presented through median and interquartile range (25% to 75%). Comparisons were performed between patients in the NA and non-NA groups for consistency among subpopulations with χ^2 tests for nominal variables and *t* tests for continuous variables. Follow-up started at diagnosis and ended at the date of last news or date of death, and the median follow-up for all patients was 5 years.[1-15] The primary end point of the study was the occurrence of a secondary malignancy, either t-MDS/AML or histologic transformation to aggressive NHL, and was calculated as a cumulative probability or as a cumulative incidence of secondary events. Cumulative probability was calculated using the Kaplan-Meier estimate in which the data of patients who died were censored and in which curves were compared using the log-rank test. Effects of potential risk factors on secondary events rates were examined in a Cox proportional hazards model. All statistical tests were two-sided. All analysis was conducted in SPSS software (SPSS Inc, Chicago, IL).[15]

Table 1. Characteristics of Patients Treated With NA Compared With Patients Treated Without NA and Untreated Patients

Characteristic	NA		Non-NA			Untreated	
	Median	Range	Median	Range	*P**	Median	Range
Total patients							
No.	193		136			110	
%	44		31			25	
Age at diagnosis, years	57	34-80	59	33-83	.09	60	40-87
Serum IgM level, g/L	26.5	2-94	34.4	7-124	.28	22	7-55
β2-microglobulin, mg/L	3	1-13	2.7	1-13	.10	2.3	1-11
Albumin, g/L	43	33-52	45	35-52	.10	45	35-52
BM involvement, %	35	4-90	40	5-90	.75	20	2-90
Hemoglobin, g/dL	11.5	6-16	11.5	8-16	.89	12.6	8-17
Platelet, $\times 10^9$/L	222	11-608	251	66-613	.35	263	150-675
WBC, $\times 10^9$/L	5	0.7-13.7	6.3	1.7-22	.10	6.6	2.2-14
Lymphadenopathy					.36		
No.	30		19			11	
%	16		14			10	
Hepatosplenomegaly					.46		
No.	15		12			—	
%	8		9				
Familial history†					.16		
No.	44		24			23	
%	23		18			21	
Therapy history							
Median no. of treatments	2		2		.51	—	
Other treatments, %							
Chlorambucil	22		22		.62	—	
Cyclophosphamide-based regimens	27		26		.23	—	
Monoclonal antibodies‡	80		95		.14	—	
Immunomodulators§	10		8		.10	—	
Follow-up from onset of first therapy, years	6	1-14	5	1-12	.29	—	—
10-year survival from onset of therapy, %‖	55	1-10	93	2-12	.001	—	—

NOTE. Data provided are at time of initial presentation and at which point treatment decisions were made.
Abbreviations: NA, nucleoside analogs; IgM, immunoglobulin M; BM, bone marrow.
*P value from comparison of NA to non-NA groups.
†Familial history of B-cell malignancies among first-degree relatives.
‡Alemtuzumab or rituximab.
§Thalidomide or lenalidomide.
‖Determined by Kaplan-Meyer estimate.

RESULTS

Patient Characteristics and Survival

Characteristics of patients with (NA) compared with patients treated without NA (non-NA) provided at time of initial presentation and at which point treatment decisions were made, along with characteristics of untreated patients, are summarized in Table 1. The male to female ratio in the three groups was 1:5, 1:4, and 1:7, respectively. There were no significant differences between NA- and non-NA–treated patients with respect to the characteristics of the WM disease, especially with regard to adverse prognosis and tumor burden markers. There was no significant difference regarding the use of chlorambucil, cyclophosphamide-based regimens, immunomodulators, and monoclonal antibodies between these two groups, and less than one third of the patients had received chlorambucil in the non-NA group. The NA treatment characteristics in the NA group are summarized in Table 2. Most patients in the NA cohort received NA-based therapy as front-line therapy (n = 115; 60%), and most received fludarabine as their NA (n = 136; 70.5%).

Incidence of Transformation and t-MDS/AML Events

Twelve patients (6.2%) had either a transformation (n = 9; 4.7%) or developed t-MDS/AML (n = 3; 1.6%) in the NA group, whereas only one patient (0.4%) developed transformation in the non-NA group ($P < .001$), and none were observed in the untreated group ($P < .001$). The 15-year probabilities of developing either transformation or t-MDS/AML were 21% and 8%, respectively, for NA-treated patients. The median time from diagnosis and onset of NA therapy to occurrence of transformation was 6 years (range, 1 to 14 years) and 5 years (range 0 to 14 years), respectively (Fig 1A). The characteristics of the transformation events are described in Table 3. Overall, the predominant transformed histology was of a diffuse large B-cell lymphoma type (DLBCL) for eight patients in the NA group and one patient in the non-NA group. One case of transformation to Hodgkin's disease was observed in the NA group. The majority of the patients who developed transformation had involvement of extramedullary sites, and transformation involving the BM was observed in three patients (33%). One patient with DLBCL refused treatment and consequently died of transformation. Of the eight remaining patients with DLBCL, five patients were treated with cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (CHOP-R), and three (60%) of these patients reached complete remission (CR). One patient, who had a partial response to CHOP-R, subsequently received autologous stem-cell transplantation and achieved a CR. Three of eight patients who developed transformation received radiotherapy for localized disease, of whom two patients experienced relapse; one patient had relapse in a different site and reached CR after undergoing local radiotherapy at the second involved site, whereas the second patient received CHOP-R and achieved a CR. Overall, six of eight patients who underwent systemic treatment for their DLBCL transformation, either with CHOP-R or with CHOP-R followed by consolidating autologous transplantation, achieved a CR for their transformed disease. One patient who transformed to Hodgkin's disease was treated with doxorubicin, bleomycin, vinblastine, and dacarbazine and achieved a durable CR. Thus most patients who demonstrated transformation were effectively treated with salvage therapy.

The incidence of MDS/AML and transformation events was not statistically different in patients treated with NA as first-line treatment versus patients treated later in their disease history (Table 4,

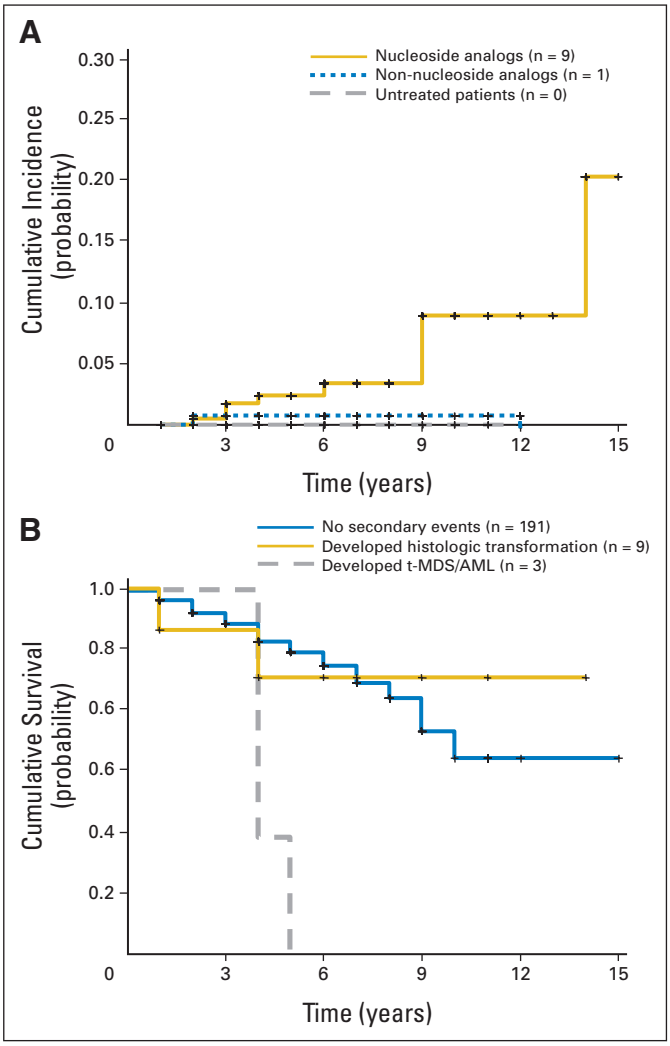

Fig 1. (A) Cumulative incidence of transformation events in the three groups. (gold line), Nucleoside analog (NA)–treated group (n = 9); (blue dotted line), non-NA–treated group (n = 1); (gray dashed line), untreated patients (n = 0). (B) Survival from onset of NA treatment for patients treated with NAs (blue line) without secondary events (n = 191) and (gold line) those who developed histologic transformation (n = 9) or (gray dashed line) therapy-related myelodysplastic syndrome/acute myeloid leukemia (n = 3).

Table 2. Characteristics of the NA Therapy in the NA Group

Characteristic	No.	%
Type of NA		
Fludarabine	136	70
Cladribine	48	25
Both	9	5
Retreatment with NA	26	13.5
First-line therapy	115	60
Time from diagnosis to NA, months		
Median	3	
SE	2	

Abbreviation: NA, nucleoside analogs.

Table 3. Characteristics of Patients Who Developed Transformation in NA (n = 9) and Non-NA Groups (n = 1)

Group	Patient	Oral Alkylator*	WM†	Transformation Disease					Follow-Up (months)
				Localization	Histology	Regimen	Response	Status	
NA	1	Yes	Stable	ADP	DLBCL	CHOP-R × 6	CR	Alive	60+
NA	2	No	Progression	BM	DLBCL	CHOP-R × 8	CR	Dead	15
NA	3	No	Progression	BM + ADP + orbits	DLBCL	CHOP-R × 6+ local Rx ICE × 2-ASCT	PR CR	Alive	20+
NA	4	No	Stable	Femur-lumbar	DLBCL	Local Rx	CR	Alive	75+
NA	5	Yes	Slowly progressing	Orbits bilateral	DLBCL	Local Rx CHOP-R × 4	Relapse CR	Alive	10+
NA	6	No	Stable	BM	DLBCL	—	—	Dead	3
NA	7	No	Progression	ADP + bulky mass	DLBCL	Rx + CHOP-R × 6 Non myeloablative allotransplantation	Relapse CR	Alive	12+
NA	8	Yes	Stable	Sinus	DLBCL	Rx Rx	Relapse CR	Alive	16+
NA	9	No	Stable	ADP + chest	Hodgkin's	ABVD × 8	CR	Alive	23+
Non-NA	10	No	Progression	ADP	DLBCL	CHOP-R × 6	CR	Alive	13+

Abbreviations: NA, nucleoside analogs; WM, Waldenström macroglobulinemia; ADP, adenopathy; DLBCL, diffuse large B-cell non-Hodgkin's lymphoma; CHOP-R, cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab; CR, complete remission; BM, bone marrow; Rx, radiotherapy; PR, partial response; ICE, ifosfamide, carboplatin, and etoposide; ASCT, autologous stem-cell transplantation; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine.
*Patients received oral alkylators throughout their disease history.
†Status of WM disease at time of diagnosis of transformation.

left column), in patients treated with either one or with multiple courses of an NA (Table 4, middle column), and in patients with history versus no history of treatment with an oral alkylating agent (Table 4, right column).

Among the three patients who developed t-MDS/AML in this series, only one patient (patient 1) had previously received oral alkylator therapy (chlorambucil). The cytogenetic patterns using conventional karyotyping for these three patients were as follows: patient 1, 46 XY, +1, der(1,7)(q10;p10); patient 2, 46, X, −Y; and patient 3, 44, XY, der(5), t(5;12)(q13;q13), −7, −12. WM disease for these three patients was in remission at time of diagnosis of t-MDS/AML.

t-MDS/AML But Not Transformation Events Are of Poor Prognosis in Patients With WM Treated With NAs

With a median follow-up of 5 years (range, 1 to 14 years), 54 patients died in this series, including four (3.6%), nine (7%), and 41 patients (21%) in the untreated, non-NA, and NA groups, respectively. Of the 41 patients in the NA group who died, 20 died of WM and related complications, such as infection, bleeding complications, and progression of the disease. The median overall survival was not reached for the three groups, though it was lower in the NA group ($P = .001$). The 10-year probability of survival was 88%, 83% and 67% in the three groups, respectively. Of the nine patients who developed transformation in the NA group, only two patients (22%) died, and the median survival from onset of NA therapy for this group was not reached, compared with NA-treated patients who did not develop transformation ($P = .72$) (Fig 1B). The 10-year probability of survival from onset of NA therapy in the transformed and nontransformed NA groups were 76% and 54%, respectively. All three patients who developed t-MDS/AML succumbed at a median of 5 months (range, 4 to 5 months).

Assessment of Risk Factors for Development of Transformation or t-MDS/AML

We next examined several risk factors to predict for the occurrence of transformation and/or t-MDS/AML given their prognostic

Table 4. Incidence of MDS/AML and Transformation in Patients With NAs

Event	NA, First Line					Re-Treatment With NA					History of Treatment With Oral Alkylating Agent				
	No		Yes			No		Yes			No		Yes		
	No.	%	No.	%	*P*	No.	%	No.	%	*P*	No.	%	No.	%	*P*
All events*	6	7.7	6	5.2	.50	11	6.6	1	3.8	.53	5	5.0	7	7.5	.47
Transformation†	5	6.4	4	3.4	.37	8	4.9	1	3.8	.80	3	3.0	6	6.4	.27
10-year estimate from onset of therapy, %															
All events*	84		91		.38	86		95		.30	91		88		.72
Transformation†	86		94		.30	89		95		.45	94		89		.46

Abbreviations: MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; NA, nucleoside analog.
*Including AML/MDS and transformation to other lymphoma.
†Transformation to other lymphoma.

significance in previous studies:[1,2] sex, age, family history of hematologic malignancies in first relatives, markers of tumor burden (BM involvement, serum immunoglobulin M level [40 g/L], serum viscosity level [1.8 cP]), prognosis markers (β2-microglobulin [3 mg/L], cytopenia [anemia, 10g/dL; WBC, 4×10^9/L; platelets, 100×10^9/L]; age, 65 years), and characteristics of the NA treatment (re-treatment with NA, type of NA therapy [2-chlorodeoxyadenosine *v* fludarabine], time from diagnosis to NA, NA at front-line or relapse setting, and treatment with oral alkylator/chlorambucil). None of these factors significantly predicted for the occurrence of transformation and/or t-MDS/AML events for patients with WM treated with NA. However, no definite conclusion can be drawn because of the low number of transformation (n = 9) and t-MDS/AML (n = 3) events, and therefore, a lack of power in multivariate analysis might also explain that no risk factors except treatment with NA were observed.

DISCUSSION

The NAs fludarabine and 2-chlorodeoxyadenosine are widely used in the treatment of WM and are recommended as either front-line or salvage agents in guidelines.[1,2] However, caution with the use of these agents has been recommended out of concern for possible stem-cell damage and potential occurrence of other adverse events, including disease transformation, MDS, and AML.[1] We therefore studied the incidence of histologic transformation and occurrence of t-MDS/AML in a large series of patients with WM.

We observed a significantly higher incidence of disease transformation and t-MDS/AML in patients treated with NA, with the occurrence of transformation being three times greater than that of t-MDS/AML. The occurrence of histologic transformation to DLBCL has been reported previously in WM either as anecdotal reports[5] or as a complication after treatment with NAs and chlorambucil,[7-10] as well as in a retrospective analysis of 98 patients with WM.[6] No etiology has been proposed, although treatment with NA was suspected, with or without associated alkylating agent treatment. The implication of Epstein-Barr virus in transformation has been ruled out.[6] Interestingly, the median time to development of disease transformation was more than 3 years in the majority of these smaller series, which is in line with the 5-year median time to development of transformation observed in our series. We cannot rule out that occurrence of transformation might have been related to combination of NAs and oral alkylator, at least for some patients, or to development of a more aggressive disease process independently of the treatment received.

Importantly, the outcome of the patients who developed transformation was good in our series, as only two of nine patients died from their transformation, and median survival for this subgroup did not differ from other NA-treated patients. This most likely reflected effective salvage therapy with CHOP-R. Similarly, effective salvage treatment with rituximab-based chemoimmunotherapy has been demonstrated in patients with CLL with Richter's transformation.[16,17]

The incidence of t-MDS/AML in this series was 1.6%. In a large series of patients with CLL previously treated with NA alone, the incidence was reported to be 0.5% and was even higher (3.5%) for patients treated with NA in combination with alkylators.[12] Although the mechanism explaining the possible increase in leukemogenesis after NA agents is speculative, it does not seem in this series to be a consequence of combined NA and alkylator therapy, as only one of three patients received previous alkylator treatment. The median survival after diagnosis of t-MDS/AML was short in this series at 5 months, which is in line with survival durations previously observed for patients who developed therapy-related AML in another series after NA therapy.[12] The cytogenetic patterns using conventional karyotyping demonstrated complex karyotypes with loss of the long arm of chromosome 7 in two patients and loss of chromosome 5 in one patient. The loss of chromosomes 7 and 5, as well as chromosome X, have been reported in patients with t-MDS/AML in other series after NA therapy.[12,18-20]

Our data therefore demonstrate an increased incidence of disease transformation to aggressive NHL, as well as development of t-MDS/AML, among patients with WM treated with NA. No prognostic factors could be identified in this series to predict for transformation or development of t-MDS/AML after NA therapy, although the power of the Cox models to identify predictors of transformation and MDS/AML was limited because of the low number of events isolated in our study overall. An important recognition in this study was the effective salvage treatment of patients developing transformation with CHOP-R and the observation that the median survival of patients developing NA-related transformation did not differ from that of other NA-treated patients with WM after salvage therapy for transformed disease. In view of these data, we suggest that guidelines recommending NA therapy for patients with WM be updated to reflect the increased risk of disease transformation and development of t-MDS/AML. These NA treatment-associated risks should not by themselves be used to justify avoidance of NA therapy for all patients with WM, but should be used in considering risk versus benefit for a particular patient, given the expanding options of therapy for patients with WM.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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