Treatment-related myelodysplasia following fludarabine combination chemotherapy

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Although myelodysplasia (MDS) and secondary acute myeloid leukemia (sAML) are rare following fludarabine monotherapy, the risk of these diseases may potentially be increased when fludarabine is combined with cyclophosphamide or mitoxantrone due to synergistic effects on the inhibition of DNA repair. Among 137 patients treated with fludarabine combination regimens, ten patients developed MDS/sAML, including one who had received no other therapy. Six patients had abnormalities of chromosomes 5 and/or 7. The crude rate of MDS/sAML was 2.5% for previously untreated patients, and 9.3% for pretreated patients (p=0.28). The rate of MDS/sAML following fludarabine combination therapy is higher than that previously reported for fludarabine monotherapy.

Key words: purine analog, chemoimmunotherapy, chronic lymphocytic leukemia, follicular lymphoma, Waldenström's macroglobulinemia.

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Myelodysplasia (MDS) and secondary acute myeloid leukemia (sAML) are well-recognized complications of therapy with alkylating agents and topoisomerase II inhibitors.[1] A recent comprehensive review of reported MDS/sAML rates concluded that up to 10% of patients treated for non-Hodgkin's lymphoma (NHL) using either conventional dose alkylator-based regimens or high-dose therapy develop MDS or sAML within a decade of primary therapy.[2] As the median survival of selected patients with chronic lymphocytic leukemia (CLL), follicular lymphoma and other indolent lymphoid malignancies may exceed 10 years, the risk of therapy-related MDS/sAML is an important consideration in the initial choice of therapy in these conditions. Fludarabine is a purine analog that has significant activity as a single agent in CLL[3] and indolent NHL.[4] In contrast to the published experience with alkylating agents, MDS and sAML are rarely reported following fludarabine monotherapy: no such cases were reported in three large cohorts of patients receiving fludarabine as initial therapy for CLL,[5-7] and only a single case was recorded among 724 patients receiving fludarabine as salvage therapy for CLL.[8] Although there is less extensive experience with the use of fludarabine monotherapy for the treatment of indolent NHL, the incidence of MDS/sAML appears similarly low, with no cases reported in the largest published series.[4,9,10] However, the combination of fludarabine with cyclophosphamide or other DNA damaging agents may increase the risk of MDS/sAML due to synergistic effects in the induction and inhibition of DNA damage. The capacity of fludarabine to inhibit DNA repair following DNA damage is well-recognized in malignant cells lines,11 and observations of similar effects on normal lymphocytes12 raise the possibility of cumulative genetic damage in hematopoietic stem cells. In order to define the risk of MDS/sAML following fludarabine combination therapy, we examined all such cases among consecutive cohorts of patients receiving either fludarabine-cyclophosphamide (FC), FC and rituximab (FCR) or FC-mitoxantrone and rituximab (FCMR) at the Peter MacCallum Cancer Center.

Design and Methods

Between October 1996 and June 2005, 137 patients received fludarabine combination chemotherapy with either FC (n=65; F 25 mg/m^2 dailyx3, C 250 mg/m^2 daily x 3), FCR (n=66; FC with R 375 mg/m^2 on day 1) or FCMR (n=6; FCR with M 10 mg/m^2 day 1) as initial (n=40) or salvage therapy (n=97) for CLL, follicular NHL or other indolent lymphoid malignancies. Details of the treatment protocols have been previously reported.[13,14] Following completion of therapy, all patients received ongoing follow-up by clinical assessment and disease-appropriate investigations through the Peter MacCallum Cancer Center. Patients with CLL or NHL involving the bone marrow underwent bone marrow aspirate and biopsy following therapy to document disease response. Indications for bone marrow examination during remission included suspected disease recurrence, an abnormal peripheral blood smear

and/or unexplained cytopenias. In the absence of clinical or peripheral blood findings suspicious of myelodysplasia, cytogenetic studies (including fluorescent *in situ* hybridization) were performed only as required for the management of the lymphoproliferative disorder.

The case records of all patients who developed MDS/AML following therapy were reviewed. All diagnostic material was reviewed by a hematopathologist expert in the diagnosis of myelodysplastic disorders (*DAW*), and classified in accordance with the WHO Classification. In addition, when possible cytogenetic assessment was performed by the state reference cytogenetic laboratory. The international prognostic scoring system (IPSS) for myelodysplastic syndrome was calculated using published criteria.[15] As this was a retrospective quality-assurance activity involving assessment of complications arising out of standard therapy at our institution, institutional board review and patient consent were not required. Categorical data were compared using Fisher's exact test or the χ^2 test, and continuous variables were compared using the unpaired t-test or Mann-Whitney's test, as appropriate. The actuarial risk of the occurrence of MDS/AML was estimated using the method of Kaplan and Meier. All reported *p*-values are two-sided.

Results and Discussion

The median age of the cohort was 59 years (range, 30 to 89 years). Forty (29%) patients had received no prior therapy, and 97 (71%) had been previously treated. For pretreated patients, the median number of prior therapies was two (range, 1 to 10). The median time from diagnosis to fludarabine combination therapy was 36 months (range, 1 to 324). Other baseline parameters are presented in Table 1.

MDS/sAML risk and associations

The median follow-up from completion of treatment for the entire cohort was 40 months (range, 5 to 86 months), and at least 12 months follow-up was available for 97% of the patients. During this period, ten patients developed MDS/sAML (crude rate 7.3%). When analyzed by Kaplan-Meier analysis, the risk of MDS/sAML at the median follow-up was 6%; this compared with a 28% risk of death as a direct consequence of the underlying lymphoid malignancy (Figure 1). Nine out of the ten patients who developed MDS/sAML had received other therapies prior to their exposure to the fludarabine combination regimen. No significant difference was found in the risk of MDS/sAML between previously untreated and pretreated patients in this small sample when analyzed by crude rate (untreated 2.5% vs pretreated 9.3%, p=0.28) or by time-to-event analysis (log rank p=0.14). There was, however, a trend to an increased MDS/sAML crude rate with increasing numbers of prior therapies (Table 1). A minority of patients had received prior axial radiotherapy (n=25), radioimmunotherapy (n=4) and/or autologous stem cell transplan-

Table 1. Baseline characteristics and cude rates of myelodysplastic syndrome/acute myelogenous leukemia (MDS/AML).

Baseline characteristics	*Number (%) (95% C.I.)*	*MDS/AML rate %*	*p value*
Age > 60 years	64 (47%)	8% (3–17%)	1.0 (v age ≤60)
Male sex	90 (66%)	4% (2–11%)	0.09 (v female)
Time from diagnosis > 36 months	68 (50%)	10% (5–20%)	0.21 (v ≤36 months)
Number of prior therapies			
no prior therapy	40 (29%)	2.5% (0–13%)	0.28 (v pretreated)
1 to 2 prior therapies	54 (39%)	6% (2–15%)	0.11[a] (no v 1-2 v 3+)
3 or more prior therapies	43 (31%)	14% (7–27%)	0.04[b] (no v 1-2 v 3+)
Prior axial radiotherapy (RT)	25 (18%)	8% (2–25%)	1.0 (v no RT)
Prior autologous BMT	7 (5%)	29% (9–65%)	0.08 (v no ABMT)
Prior radioimmunotherapy (RIT)	4 (3%)	25% (5–72%)	0.26 (v no RIT)
Chronic lymphocytic leukemia (CLL)	52 (38%)	2% (0–10%)	0.09 (CLL v others)
Follicular lymphoma (FL)	48 (35%)	15% (7–27%)	**0.03** (FL v others)
Mantle cell lymphoma	11 (8%)	0% (0–26%)	
Waldenström's macroglobulinemia	16 (12%)	13% (4–36%)	**0.05**[a] (CLL v FL v others)
Other indolent lymphoproliferative	10 (7%)	0% (0–28%)	
Fludarabine Cyclophosphamide (FC)	65 (47%)	9% (4–19%)	0.52 (FC v FCR/FCMR)
FC-Rituximab (FCR)	66 (48%)	2% (0–8%) (FCMR v FC/FCR)	**0.005**[c]
FC-Mitoxantrone Rituximab (FCMR)	6 (4%)	50% (18–82%)	
> 4 cycles FC/FCR/FCMR	44 (32%)	7% (2–18%)	1.00 (v 4 cycles)

BMT: bone marrow transplantation; [a]χ^2 test for independence; [b]χ^2 test for trend; [c]Note association between follicular lymphoma and FCMR (p=0.02).

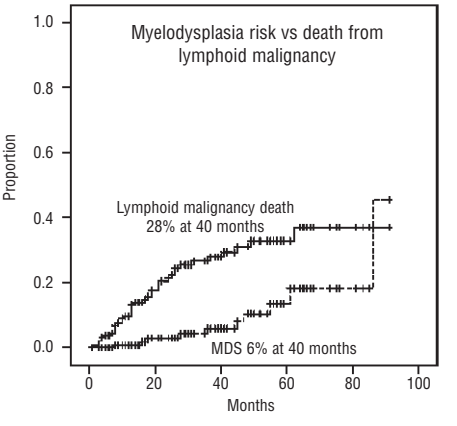

Figure 1. Actuarial risk of myelodysplasia/acute myelogenous leukemia (MDS/AML) occurrence and death related to lymphoid malignancy. Median follow-up was 40 months for the entire cohort.

Table 2. Patients with treatment-related myelodysplasia (MDS) following fludarabine combination therapy.

	Age & sex histology	*Previous therapies*	*Regimen and time to MDS/AML*	*WHO category and cytogenetics*	*IPSS*	*Outcome*
UPN1	56-year old male Waldenström's macroglobulinemia	Nil	FC×10 86 months	Chronic myelomonocytic leukemia (I) 46,XY,del(13) (q12q22) [20]	0.5	Alive at 16 months with stable MDS
UPN2	40-year old female Follicular lymphoma	CVP CNOP BEAM-AuBMT	FC×4 55 months	Refractory cytopenia with multilineage dysplasia, 46,XX,+1,der(1;7)(q10;p10) [17]/46,XX,del(5)(q21q31) [7]/46,XX [14].	1.0	Died at 25 months following progression to RAEB-1.
UPN3	53-year old female Follicular lymphoma	CVP CEP Chlorambucil Mitoxantrone CHOP Etoposide	FC×5 47 months* *ICE & BEAM-ABMT after FC	Refractory cytopenia with multilineage dysplasia, 46,XX [20]	0.5	Alive at 30 months with stable MDS.
UPN4	53-year old male Follicular lymphoma	Chlorambucil	FCMR×4 45 months	Chronic myelo-monocytic leukemia (I) 45,XY,del(2)(p11p14),del(7) (q22),dic(3;7)(p11;p13), -15, der(?)t(?;3)(?;p13)[20]	1.0	Died at 15 months following progression to AML.
UPN5	66-year old female Follicular lymphoma	Axial RT Chlorambucil CEP	FCMR×4 8 months	Refractory cytopenia with multilineage dysplasia. Cytogenetics not done.	n/a	Died at 2 months from neutropenic sepsis.
UPN6	65-year old male Follicular lymphoma	Chlorambucil CNOP Mel-AuBMT BEAM-AuBMT	FC×3 18 months* *received axial RT after FC	Refractory cytopenia with multilineage dysplasia. Cytogenetics not done.	n/a	Died at 8 months from progressive lymphoma, with stable MDS.
UPN7	60 year-old female Waldenström's macroglobulinemia	Chlorambucil CVP	FC×4 61 months	Acute myeloid leukemia with multilineage dysplasia. 39-40,XX,add(1)(q32),-3, add(5)(q31),add(7)(p22),-10, add(12)(p11),der(13;21) (q10;q10),-15,add(16)(q24), add(17)(p13),-21,-22[cp2]	n/a	Alive at 3 months with persistent AML following chemotherapy.
UPN8	69-year old male Follicular lymphoma	Chlorambucil I^{131}anti-CD20	FCR×3 16 months	Refractory cytopenia with multilineage dysplasia 46,XY,del(7)(q22)[12]/46,XY[18]	1.5	Died at 17 months from large cell lymphoma, with stable MDS.
UPN9	52-year old female Follicular lymphoma	CHOP	FCMR×4 28 months	Refractory cytopenia with multilineage dysplasia 45,XX,-7[13]/46,idem,+mar[5] /46,XX[19]	1.0	Died at 21 months following progression to RAEB-2.
UPN10	66-year old female Chronic lymphocytic leukemia	Cyclophosphamide CHOP Etoposide FND Axial RT	FC×4 FCR×3 36 months	Refractory anemia with excess blasts (I) 44-45,XX,?dic(5;17) (q?11;p?13),del(7)(q22),add (8)(p23),add(12)(p13),-13, +mar1[cp13]/88-90,idemx2 [cp2]/44,XX,?dic(5;17),del(7) (q13),?-8,add(14)(p13),add (17)(p13)[cp2]/46,XX [2]	2.0	Died at 9 months following progression to AML.

AML: acute myelogenous leukemia; BEAM-AuBMT: autograft using carmustine, etoposide, cytarabine and melphalan conditioning; CEP: cyclophosphamide, etoposide and prednisolone; CHOP: cyclophosphamide, adriamycin, vincristine and prednisolone; CNOP: cyclophosphamide, mitoxantrone, vincristine and prednisolone; CVP: cyclophosphamide, vincristine and prednisolone; FC: fludarabine and cyclosphosphamide; FCR: FC and rituximab; FCMR: FCR and mitoxantrone; FND: fludarabine, mitoxantrone and dexamethasone; IPSS: International Prognostic Scoring System; RAEB, refractory anemia with excess blasts.

tation (n=7). No statistically significant increase in MDS/sAML risk was present in any of these small subgroup of patients. A staitistically significant association was present between MDS/sAML risk and follicular lymphoma (MDS/sAML crude rate 15% vs 3.5% for other histological subtypes, p=0.03). Among the six patients who received FCMR (median 1 prior therapy, range 1 to 3), three (50%) developed MDS/sAML, a significantly higher rate than among patients who received FCR or FC (5.3%, p=0.005). However, this observation was confounded by an association between follicular lymphoma and FCMR therapy (p=0.02). Due to the large number of variables relative to the number of events, multivariate analysis was not informative in determining the risk of MDS/sAML in relation to histology and mitoxantrone.

Characteristics and outcomes of MDS/sAML patients

MDS/sAML occurred at a median of 40 months (range 8 to 86) following fludarabine combination therapy (Table 2). Morphological diagnoses were: refractory cytopenia with multilineage dysplasia (RCMD, n=6), chronic monomyelocytic leukemia (CMML, n=2), refractory anemia with excess blasts-I (RAEB-I, n=1) and sAML (n=1). Among the nine previously treated patients who developed MDS/AML, pre-treatment bone marrow aspirate and trephine showed no morphological evidence of MDS/AML in seven patients (UPN2-UPN8); cytogenetic examination was not performed on these samples. UPN9 developed MDS with monosomy 7 but had no evidence of this abnormality when her peripheral blood stem cells (collected 2 months prior to fludarabine combination therapy) were examined with fluorescent *in situ* hybridization. UPN10 underwent bone marrow examination immediately following completion of fludarabine combination therapy and had no morphological evidence of MDS at that time. Patients with cytogenetic abnormalities at the time of the diagnosis of MDS included five patients with abnormalities in chromosomes 5 and/or 7, one patient with deletion of chromosome 13q, and one patient with diploid cytogenetics. Among these seven patients, IPSS categories were intermediate-1 (INT-1) in five and intermediate-2 (INT-2) in the other two. Two further patients with bilineal cytopenia and unequivocal morphological features of RCMD did not undergo cytogenetic study and were thus not evaluable for the IPSS. The single patient with sAML had a deletion of chromosome 7q. At a median follow-up of 16 months (range 3–30), four MDS patients had progressed to RAEB or sAML; all of these patients had abnormalities of chromosomes 5 or 7. Two were refractory to conventional induction chemotherapy and died of progressive disease. One patient underwent an unrelated allogeneic stem cell transplant and died of early complications. The last patient with progressive MDS underwent autologous transplantation using stem cells negative for her cytogenetic abnormality (deletion of chromosome 7) and experienced a transient morphologic and cytogenetic complete response, but relapsed 5 months after the autograft and died during re-induction chemotherapy. Of the remaining five MDS patients, one died of neutropenic sepsis, two died of progressive lymphoma, and two remain alive at 16 and 30 months with stable MDS. The IPSS categories were not predictive of outcome. The patient with sAML was refractory to induction chemotherapy and remains alive 3 months after diagnosis. Although our patient cohort was heterogenous in histological subtypes and prior treatment status, the crude MDS/AML rates of 9.3% for pretreated patients and 2.5% for chemotherapy-naïve patients were higher than those previously reported for similar patients receiving fludarabine monotherapy for CLL[5-8] or indolent NHL,[4,9,10] in whom the reported incidence has been less than 1%. The frequent occurrence of chromosome 5 or 7 abnormalities, similar to those observed in MDS following alkylating agent-based regimens, favors inhibition of cyclophosphamide-induced DNA damage (as demonstrated in preclinical experiments) as a putative pathogenic mechanism. Given the low number of cases, we were unable to establish the relative contribution of mitoxantrone and follicular lymphoma to the risk of MDS/AML following fludarabine combination therapy. Mitoxantrone has been implicated in the development of therapy-related myelodysplasia[16] and may contribute to the DNA damaging effects of fludarabine and cyclophosphamide. Our experience that half of patients develop MDS after FCMR therapy is likely to be an effect of small sample size and is not confirmed by the favorable experiences in larger studies using similar regimens.[17,18] Our observations of an increased risk of MDS/AML following fludarabine combination therapy are supported by recent reports from the CALGB and the M.D. Anderson Cancer Center reporting increased MDS/AML risk when fludarabine was combined with a DNA-damaging agent. Morrison *et al.*[19] reported a crude MDS rate of 3.5% among patients with CLL randomized to receive fludarabine and chlorambucil in the CALGB 9011 study, as compared with 0.5% and 0% among patients receiving fludarabine or chlorambucil alone (p=0.007). This is similar to the rate of 4% reported by McLaughlin *et al.*[20] among patients receiving fludarabine, mitoxantrone and dexamethasone (FND) as initial therapy for indolent NHL. Importantly, both of these studies primarily involved chemotherapy-naïve patients, whereas the majority of patients in the current series were previously treated. Possibly due to the relatively small number of events, no statistically significant difference in MDS/sAML risk between previously untreated and pretreated patients could be demonstrated, although analysis by the number of prior therapies does suggest a dose-exposure effect. The current study in conjunction with the reports from the CALGB and the M.D. Anderson Cancer Center indicate that the crude rate of myelodysplasia may be up to 10% among patients treated with fludarabine combination therapy; this rate is higher than that reported for fludarabine monotherapy but is not dissimilar to that expected for patients treated with alkylating agents and/or high dose therapy.[2] Importantly, the risk of death related to lymphoma remains appreciably higher than the risk of developing MDS/sAML, indicating that the choice of fludarabine combination regimens, which constitute some of the most active regimens in lymphoid malignancies,[9] remains appropriate. MDS/sAML is an important complication of fludarabine combination therapy, and clinicians should discuss this risk when recommending such therapy to patients with indolent lymphoid malignancies.

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