Brief report

Incidence of therapy-related myeloid neoplasia after initial therapy for chronic lymphocytic leukemia with fludarabine-cyclophosphamide versus fludarabine: long-term follow-up of US Intergroup Study E2997

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Chemotherapy-related myeloid neoplasia (t-MN) is a significant late toxicity concern after cancer therapy. In the randomized intergroup phase 3 E2997 trial, initial therapy of chronic lymphocytic leukemia with fludarabine plus cyclophosphamide (FC) compared with fludarabine alone yielded higher complete and overall response rates and longer progression-free, but not overall, survival. Here, we report t-MN incidence in 278 patients enrolled in E2997 with a median 6.4-year follow-up. Thirteen cases (4.7%) of t-MN occurred at a median of 5 years from initial therapy for chronic lymphocytic leukemia, 9 after FC and 4 after fludarabine alone. By cumulative incidence methodology, rates of t-MN at 7 years were 8.2% after FC and 4.6% after fludarabine alone ($P = .09$). Seven of the 9 cases of t-MN after FC occurred without additional therapy. Abnormalities involving chromosomes 5 or 7 were found in 10 cases, which suggests alkylator involvement. These data suggest that FC may induce more t-MN than fludarabine alone. (*Blood*. 2011;118(13):3525-3527)

Introduction

Therapy-related myeloid neoplasia (t-MN), including myelodysplastic syndrome and acute myeloid leukemia, is a concerning long-term toxicity, particularly because treatment outcomes for t-MN are worse than for de novo myeloid neoplasia.[1] Alkylating agent DNA damage as a cause of t-MN has a defined peak risk period of 3-8 years after treatment and is often characterized by specific abnormalities of chromosomes 5 and 7.[2] Topoisomerase II inhibitors induce t-MN with shorter latency and abnormalities of 11q23,[3] the MLL gene locus. Nucleoside analogs have been associated with t-MN, although rates are less clear, with no specific cytogenetic abnormality.[4]

Alkylating agents and nucleoside analogs are important classes of therapeutic agents in chronic lymphocytic leukemia (CLL). The occurrence of t-MN has been reported at a higher frequency with chlorambucil plus fludarabine than with fludarabine alone,[5] but this has not been studied rigorously in the context of cyclophosphamide as an alkylating agent. Fludarabine alone and fludarabine in combination with cyclophosphamide (FC) are commonly used therapeutic regimens for CLL[6,7] and provide the backbone of widely used chemoimmunotherapy with the addition of rituximab (FCR). The intergroup, prospective, randomized phase 3 trial E2997 compared FC with fludarabine alone as initial CLL therapy in the pre-rituximab era. FC yielded higher complete and overall response rates and longer progression-free survival in the initial analysis.[8] One rationale for combining fludarabine with cyclophosphamide is that fludarabine inhibits repair of cyclophosphamide-induced DNA damage. As expected, FC caused more myelosuppression than fludarabine alone, which could lead to more serious long-term effects on myelopoiesis, including t-MN.[9] Indeed, with 6.4 years of follow-up, our data suggest a higher incidence of t-MN after FC than after fludarabine alone.

Methods

As reported previously, E2997 enrolled 278 patients with previously untreated CLL that required therapy, with 141 randomized to FC and 137 to fludarabine alone, without rituximab.[8] Patient demographics were well balanced. Briefly, median age was 61 years, 70% were male, and 84% had performance status 0-1. Cyclophosphamide 600 mg/m^2 was given on day 1 of each FC cycle. All patients in the FC arm were assigned to receive filgrastim support, whereas only 25 received any filgrastim in the fludarabine-alone arm, only 1 of whom developed t-MN. Cases were assessed for t-MN by required reporting of these events to the Eastern Cooperative Oncology Group, the coordinating center for this study, through the Adverse Event Expedited Reporting System (ADEERS) mechanism. Baseline interphase FISH and immunoglobulin heavy chain gene (IgV_H) mutation analysis of CLL, available for 235 patients, 122 given FC and 113 given fludarabine alone, were balanced, with 8% del17p and 47% unmutated IgV_H in each arm.[10] Given the small numbers, no relation of CLL FISH and t-MN was apparent.

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Table 1. Details of t-MN patient demographics, treatment, and outcome

Patient	Tx arm × no. of cycles	Age (y) at study entry/sex	IgV_H mutation status	CLL FISH	CLL response	Additional therapy	Time to t-MN, mo	Survival after t-MN, mo	t-MN cytogenetics
1	FC × 4	69/Male	Mutated	13q−	CR		59	17	46,XY,−6,add(7)(q22),del(20)(q11.2q13.1),+mar[4]/47,XY,add(9)(q13),add(10)(p11.2),+11[cp4]/46XY[12]
2	FC × 6	57/Male	Mutated	13q−, +12	PR		85	1	Not tested
3	FC × 6	47/Male	Mutated	Normal	PR		72	6	46,XY,del(5)(q13q33),−7,t(7;10)(q35;q22),i(8)(q10),del(11)(q22q25),der(11)invdup(11)(25q13)dup(11)(q13q25),add(17)(p13),del(17)(q23q25),+mar[18]/46,XY[2]
4	FC × 6	64/Female	Not tested	Not tested	CR		25	13	45,XX,der(5)t(5;12)(q10;q11),del(7)(q32q34),−12,del(13)(q12)[16]/45,XX,der(5)t(5;12)(q10;q11), del(7)(q32q34),der(12)t(12;13)(q10;q21),13[8]/46,XX,−5,+8,del(13)(q12)[4]/46,XX[7]
5	FR × 6	60/Female	Mutated	13q−	PR		39	7	44−48,XX,del(3)(p23),add(5)(q11.2),dic(21;?)(q22;?),+0−2mar[cp15]/46,XX[5]
6	FC × 6	70/Female	Not tested	Not tested	PR	Alkylators	72	7+	47−48,XX,−2,−8,add(11)(p15),+22,+2−4mar,inc[cp7]/46,XX[6]
7	FC × 2	68/Male	Mutated	13q−; 17p−	PD	Etoposide; others	65	9+	42,XY,−4,der(7)t(7;8)(p22;q13),−8,add(17)(p13),−20,−21[cp4]/46,XY[9]
8	FC × 6	80/Male	Mutated	Normal	CR		40	20	45,XY,−7,del(12)(p11.2)[cp10]/47,XY,+8[2]/46,XY[8]
9	FC × 6	51/Male	Mutated	13q−	PR		61	1+	45,XY,−7[17]/46,XY[3]
10	F × 1	58/Male	Not mutated	13q−; 11q−	Unknown	FR	84	4	45,XY,t(3;8)(q23;p23.1),der(5)t(5;7)(q13;p13),−7,del(13)(q21.2q22)[20]
11	F × 6	45/Male	Not mutated	14q; +12	PR	FCR; NMSCT	73	12+	47,XY,+add(12)(q13),t(14;19)(q32;13.3)[4]/46,XY[6]
12	F × 6	76/Female	Mutated	13q−	PR		8	30	46,XX,+1,der(1;15)(q10;p10)[6]/46,XX[24]
13	F × 6	56/Male	Not mutated	13q−	PR	Alkylators; other	72	10+	47,XY,add(7)(q11.2),del(20)(q11.2q13.3),+21[18]/46,XY[2]

Tx indicates treatment; CR, complete response; PR, partial response; F, fludarabine alone; PD, progressive disease; and NMSCT, nonmyeloablative stem cell transplantation.

Results and discussion

Ongoing monitoring of E2997 toxicity revealed a significant incidence of t-MN. With median follow-up currently 6.4 years, 13 cases (4.7%) of t-MN, 9 after FC and 4 after fludarabine alone, have been reported (Table 1). By cumulative incidence methodology, with adjustment for competing risks of death, the rates of t-MN at 7 years were 8.2% after FC and 4.6% after fludarabine alone ($P = .09$, 1-sided Gray test). Increasing age is a risk factor for developing t-MN, but median age at study entry of the patients who eventually developed t-MN was 60 years (range 45-80 years) versus 61 years (range 33-86 years) for those not developing t-MN. The median time from initial therapy to diagnosis of t-MN (5 years; range 0.7-8 years) did not differ between treatment arms. Ten of the 13 t-MN patients received the planned 6 chemotherapy cycles. Of the 3 who received fewer cycles, 1 achieved complete remission with 4 cycles of FC and stopped treatment because of rash, 1 had CLL progression after 2 cycles of FC, and 1 was removed from the study after 1 cycle of fludarabine alone because of a concurrent diagnosis of mycosis fungoides. Additional therapy before occurrence of t-MN was given to only 2 of 9 FC patients in contrast to 3 of 4 patients given fludarabine alone. Additional therapy in the 3 fludarabine-alone patients was fludarabine alone plus rituximab as 2 separate courses in 1 patient, FC-rituximab followed by nonmyeloablative sibling donor stem cell transplantation in a second, and multiple agents including alkylators in the third.

Thus, t-MN occurred in only 1 patient treated with fludarabine alone (patient 12 in Table 1) as opposed to 7 of those who received FC and no further therapy. Ten of 12 patients with available cytogenetics on diagnosis of t-MN had an abnormality of chromosome 5 and/or 7, common to alkylating agent–induced t-MN, usually (n = 8) in the context of a complex karyotype, with 1 patient each having only 45,XY, −7 and 45,XY, −7, del(12)(p11.2). In the fludarabine-alone arm, patient 10 had abnormal chromosomes 5 and 7 despite receiving no alkylators, whereas 2 patients had abnormal cytogenetics not involving chromosome 5 or 7, 1 of which was consistent with residual CLL. Of the 9 who developed t-MN after FC, all 7 with available CLL IgV_H mutational status data had lower-risk mutated IgV_H, in contrast to 1 of the 4 with t-MN after fludarabine alone and 44% in the entire cohort[10] (Table 2). Despite the higher likelihood of extended remission with mutated IgV_H, median time to t-MN in the 3 patients with unmutated IgV_H after fludarabine alone was 72 months.

Prior reports of t-MN after initial therapy of CLL using fludarabine-based regimens include the MD Anderson experience.[11] Of 300 patients with median age 57 years, 8 t-MN cases occurred, for an incidence of 2.8% at 6 years. A recent update of the Cancer and Leukemia Group B (CALGB) 9712 study (CALGB9712),

Table 2. Summary of incidence and clinicobiologic parameters of t-MN in E2997

			Additional therapy		IgV_H gene		
Therapy	N	t-MN	No	Yes	Mutated	Unmutated	Not tested
FC	141	9	7	2	7	0	2
F	137	4	1	3	1	3	0

which administered fludarabine-rituximab to 104 patients, reported no t-MN after median follow-up of 107 months, although 1 patient developed MDS after receiving FC plus rituximab on relapse from fludarabine-rituximab. In a series of 61 patients treated with FC plus rituximab,[9] with a median 41 months of follow-up, estimated incidence was 6.4% at 5 years. In the CALGB9011 trial, which reported a 50-month median follow-up,[5] there were no cases of t-MN among patients treated with chlorambucil alone, 1 case (0.5%) among 188 patients treated with fludarabine alone, but 5 cases (3.%) among 142 patients treated with the combination of fludarabine plus chlorambucil. Compared with the CALGB, our experience reveals a higher incidence with fludarabine alone. The incidence is even higher by cumulative incidence methodology in the FC arm of the present study.

With the median time to t-MN being 5 years, this may be close to the peak incidence seen in other cases of alkylator-induced t-MN; however, longer follow-up may reveal ongoing risk. In the present study, cytogenetics/FISH analysis of t-MN suggested DNA damage. Because FC yields longer progression-free survival, most cases of t-MN after FC occur in the absence of additional chemotherapy.

Although more frequent t-MN in the setting of mutated IgV_H might reflect a surveillance bias, because new cytopenias that occur during prolonged CLL remission may prompt marrow evaluation, this is not apparent from the time to develop t-MN in the present small cohort of t-MN patients. These data emphasize the need for such surveillance.

The present analysis suggests a higher incidence of t-MN occurred after FC than after fludarabine alone in E2997. After FC, t-MN occurred most often without additional therapy and in the more favorable IgV_H mutated CLL, which suggests that FC is more mutagenic than fludarabine alone. Although the benefit of FC for high-risk del(11q22.3) CLL justifies its use in this population,[12] our observation emphasizes the need for longer follow-up of toxicity and survival before concluding that FC is preferable to fludarabine alone as the initial chemoimmunotherapy backbone for other CLL risk categories. Such concerns also emphasize the importance of deciding when to institute therapy in CLL and the ongoing need to develop less myelotoxic therapeutic agents.

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Authorship

Contribution: M.R.S and D.N. collected and analyzed the data and drafted the manuscript; I.W.F. is the principal investigator for E2997; M.R.G., H.M.L., J.M.R., J.M.B., E.M.P., J.C.B., M.A.H., F.R.A., R.A.L., M.R.L., and M.S.T. are investigators on E2997 and along with I.W.F. participated in analysis of the data and in writing the manuscript; and G.D. was responsible for the CLL FISH data.

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