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The Impact of Initial Fludarabine Therapy on Transformation to Richter's Syndrome or Prolymphocytic Leukemia in Patients with Chronic Lymphocytic Leukemia: Analysis of an Intergroup Trial (CALGB 9011)

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Abstract

The impact of initial fludarabine therapy on transformation to Richter's syndrome (RS) or prolymphocytic leukemia (PLL) in chronic lymphocytic leukemia (CLL) patients is uncertain. We studied the outcomes of 521 CLL patients who were randomized to initial fludarabine (F), chlorambucil (C), or F+C therapy on an intergroup trial (CALGB 9011). RS developed in 34 (7%) patients and PLL in 10 (2%). RS and PLL occurred in 14 (7%) and 3 (2%) of 188 patients randomized to F; 9 (5%) and 4 (2%) of 191 patients treated with C; and 11 (8%) and 3 (2%) of 142 receiving F+C, respectively. Four percent of the 286 Rai stage III/IV patients developed PLL, compared to only 1% of the 315 Rai stage I/II patients (p=0.02). Initial fludarabine therapy in CLL patients did not impact transformation to RS or PLL, nor were any other baseline characteristics predictive for such transformation in this series.

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Keywords

Richter's; Fludarabine; CLL; Prolymphocytic

Introduction

In 1928, Richter reported a case of an adult with "reticular cell sarcoma" associated with lymphocytic leukemia [1]. Four decades later Lortholary defined Richter's transformation as the development of an aggressive lymphoid malignancy in the setting of chronic lymphocytic leukemia (CLL) [2]. Other secondary lymphoid malignancies identified in CLL patients have included prolymphocytic leukemia (PLL). The incidence of transformation to Richter's syndrome (RS) ranges from 3–6% [3–5]. The impact of initial fludarabine therapy on the incidence of transformation is not known. In addition, risk factors predictive for transformation in CLL patients have not been delineated. Thus, we examined a large series of previously untreated CLL patients enrolled on a prospective intergroup study (CALGB 9011) and followed for at least 15 years to address these questions.

Patients and Methods

Five hundred forty-four patients were enrolled on an intergroup trial, "A Phase III Comparison of Fludarabine Phosphate vs Chlorambucil vs Fludarabine Phosphate + Chlorambucil in Previously Untreated B-Cell Chronic Lymphocytic Leukemia" (CALGB 9011), from October 1990 to December 1994 in the Cancer and Leukemia Group B (CALGB), the Southwest Oncology Group (SWOG), the Eastern Cooperative Oncology Group (ECOG), and the National Cancer Institute-Canada (NCI-C) Clinical Trials group. The details of this clinical trial have been previously published [6]. Eligible patients were randomized to therapy with either: Arm 1: chlorambucil 40 mg/m^2 orally on day 1, every 4 weeks; Arm 2: fludarabine, 25 mg/m^2/day intravenously, days 1–5, every 4 weeks; or Arm 3: chlorambucil 20 mg/m^2 orally on day 1 plus fludarabine 20 mg/m^2/day intravenously, days 1–5, every 4 weeks. In addition to treatment outcomes, patients were also followed for the development of second malignancies, including transformation to Richter's syndrome, which we defined for our analysis as progression of CLL to diffuse large cell lymphoma, or to PLL. Case report forms were reviewed for the occurrence of either RS or PLL, and were available for 521 of the 544 enrolled patients. Biopsy specimens were not centrally reviewed as part of this protocol.

The primary objective of the current analysis was to determine the impact, if any, of initial fludarabine, alone or in combination with chlorambucil, on the subsequent development of RS or PLL. A secondary objective was to ascertain if any baseline clinical variables were predictive for later transformation.

Statistical Methods

Univariate statistical analyses were used to examine the effect of treatment arm and other baseline patient characteristics on the probability of transformation. In all analyses, transformation was treated as a 3-level categorical variable indicating whether the patient

transformed to RS, PLL, or neither. The chi-square test was used to examine the association of categorical baseline variables with transformation. Associations of transformation with continuous predictor variables were tested by conceptually reversing the factor-response structure and using the general linear model to regress the continuous variable on transformation. Because transformation is categorical with 3 levels, all tests have 2 degrees of freedom (df), with the exception of the test of treatment arm, which has 4 df. Median time to RS (PLL) was calculated only in patients who transformed to RS (PLL). A two-sided alpha of 0.05 was used for all tests. Analyses were performed by a CALGB statistician.

Results and Discussion

All patients were followed for second malignancies, including transformation to PLL or Richter's syndrome, and survival until death or lost-to-follow-up. The median follow-up time from study enrollment was >10 years (128, 121, and 135 months in the three treatment arms (F, C, F+C), respectively). Thirty-four of 521 patients (7%) developed RS, and 10 (2%) developed PLL (Table 1). Median time to RS among RS patients was 22 months (range, 1–66); median time to PLL among PLL patients was 15 months (range, 1–36). There was no significant difference among treatment arms in the probability of transformation to either RS or PLL ($p = 0.78$). There was no difference in the transformation-free rate at 60 months among the different treatment arms ($p=0.15$).

Baseline clinical variables at study entry (age, gender, performance status, duration of CLL prior to therapy, Rai disease stage, white blood cell count, hemoglobin, lactic dehydrogenase (LDH), marrow cellularity, randomized treatment arm) were examined in univariate analyses for their association with the probability of later transformation to RS or PLL. Among these variables, only Rai stage was associated with disease transformation (2 d.f. p-value = 0.02), with this association due almost entirely to PLL (Table 1). Four percent of Rai stage III/IV patients developed PLL as compared to only 1% of Rai stage I/II patients. Six percent and 7% of Rai stage I/II and III/IV patients developed RS, respectively.

Response to initial CLL therapy was examined among patients who later developed RS and PLL. The 34 RS patients achieved the following on-study responses: CR (2), PR (5), no response (16), and unevaluable (11). Responses to initial CLL therapy in the 10 PLL patients were: CR (1), PR (4), no response (4), and unevaluable (1).

Discussion

Patients with CLL have an increased risk of second malignancies as compared to age- and sex-matched controls [7]. The rate of second malignancies among CLL patients has not appeared to change since the introduction of fludarabine therapy [8]. We previously reported, with median follow-up of 15 years, seven cases of therapy-related myeloid neoplasms in this clinical trial population [9, 10]. The reported incidence of RS ranges from 2.2–10% [3, 5, 11, 12, 13]. In one series of 1011 CLL patients, 22 cases (2.2%) of RS were found. RS was more common in patients <55 years old (12/204, 5.9%) than those >55 years (10/807, 1.2%; $p<0.0001$) [12]. Keating et al reported a cumulative 8% incidence of RS among 174 fludarabine-treated CLL patients, with time to transformation ranging from 1–62

months [14]. In another series of 185 CLL cases, the cumulative incidence of RS at ten years was 10% [13]. We observed a 6.7% incidence of RS, with most cases occurring within five years of study entry. Our study reports on a large population with prospective follow up and a very few loss to follow up. Thornton et al reported a 12% incidence of RS among 101 fludarabine-treated CLL patients and suggested that this higher incidence may be related to fludarabine-induced immunosuppression [15]. In contrast, we found the probability of RS to be comparable among fludarabine- and chlorambucil-treated patients. Response to fludarabine therapy did not impact the occurrence of RS in our series.

Prognostic factors for RS have been examined in several series. In univariate analyses with 620 CLL patients, younger age, diffuse pattern of marrow involvement, hemoglobin <12 g/dl, advanced Rai stage disease, elevated LDH, and beta-2 microglobulin >3mg/dl were predictive for Richter's transformation [14]. Age >55 years and ZAP-70 expression have also been associated with a higher risk of transformation [12]. In another series of 185 CLL patients with 17 cases of Richter's transformation, factors prognostic for such transformation at time of CLL diagnosis in multivariate analysis included CD38 expression, IGVH4–39 usage, lymph node size ≥3 cm, and the absence of del13q14 [13]. This same group found that the presence of 14q32 translocations did not confer any predisposition to RS development [16]. Others have suggested that the presence of the CD38 G-allele, which is independently associated with nodal and splenic involvement, may confer an increased risk of RS transformation, as may the presence of a stereotyped B-cell receptor [17,18]. In a large Mayo clinic CLL series, the use of purine analog therapy increased the risk of a secondary lymphoid malignancy from 1.9% to 5.2%, of which 46% were diffuse large cell lymphoma [19]. In a smaller series of Waldenstrom's macroglobulinemia patients, an increased risk of transformation to high grade lymphoma was found among patients who received purine analog therapy [20]. In our series, we identified no factors prognostic for transformation, except that CLL patients who later developed PLL were more likely to present with advanced Rai stage disease. Specifically, the initial CLL therapy, whether it was fludarabine, chlorambucil, or the combination of these two agents, had no impact on transformation to either RS or PLL. As the number of events was small in each subgroup (PLL and RS), they were pooled together in one analysis to focus on transformation as one entity.

The interval from CLL diagnosis to PLL transformation has been reported to range from two to three years [21]. Only two cases of PLL transformation were reported among 1487 CLL patients treated with cladribine or alkylating agents [22]. We found a 1.9% incidence of PLL transformation, with all cases occurring within three years of study entry.

In summary, we found no impact of initial therapy with fludarabine, as compared to chlorambucil, on the risk of transformation to either RS or PLL among CLL patients enrolled on this intergroup trial. We also found no baseline pretreatment clinical characteristics that were predictive for later RS. However, as this cooperative group trial was conducted in an earlier era, baseline demographic data routinely collected included only traditional disease- and patient-related factors, thus the impact of the newer molecular markers as CD38 or ZAP-70 expression, IGVH status, or baseline cytogenetics on transformation risk could not be assessed. Other limitation to this analysis is related to the

fact that some patients received subsequent therapies on or off protocol after their initial treatment. Some of these therapies were not captured as part of the protocol and could have affected the outcomes and transformation rates.

As new therapeutic approaches are utilized for CLL patients, their potential impact on transformation to RS or PLL warrants continued assessment.

References

1. Richter M. Generalized reticular cell sarcoma of lymph nodes associated with lymphatic leukemia. Am J Pathol. 1928; 6:285–299.
2. Lortholary P, Ripault M, Boiron M. Richter's Syndrome. Nouv Rev Fr Hematol. 1964; 72:456–457.
3. Armitage JO, Dick FR, Corder MP. Diffuse histiocytic lymphoma complicating chronic lymphocytic leukemia. Cancer. 1978; 41(2):422–427. [PubMed: 343908]
4. Foucar K, Rydell RE. Richter's syndrome in chronic lymphocytic leukemia. Cancer. 1980; 46(1): 118–134. [PubMed: 6770990]
5. Robertson LE, Pugh W, O'Brien S, Kantarjian H, Hirsch-Ginsberg C, Cork A, McLaughlin P, Cabanillas F, Keating MJ. Richter's syndrome: a report on 39 patients. J Clin Oncol. 1993; 11(10): 1985–1989. [PubMed: 8410123]
6. Rai KR, Peterson BL, Appelbaum FR, Kolitz J, Elias L, Shepherd L, Hines J, Threatte GA, Larson RA, Cheson BD, Schiffer CA. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Engl J Med. 2000; 343(24):1750–1757. [PubMed: 11114313]
7. Wiernik PH. Second neoplasms in patients with chronic lymphocytic leukemia. Curr Treat Options Oncol. 2004; 5(3):215–223. [PubMed: 15115650]
8. Tsimberidou AM, Wen W, McLaughlin P, O'Brien S, Wierda WG, Lerner S, Strom S, Freireich EJ, Medeiros LJ, Kantarjian HM, Keating MJ. Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. J Clin Oncol. 2009; 27(6):904–910. [PubMed: 19114699]
9. Morrison VA, Rai KR, Peterson BL, Kolitz JE, Elias L, Appelbaum FR, Hines JD, Shepherd L, Larson RA, Schiffer CA. Therapy-related myeloid leukemias are observed in patients with chronic lymphocytic leukemia after treatment with fludarabine and chlorambucil: results of an intergroup study, cancer and leukemia group B 9011. J Clin Oncol. 2002; 20(18):3878–3884. [PubMed: 12228208]
10. Rai K, Peterson BL, Appelbaum FR, Tallman MS, Belch A, Morrison VA, Larson RA. Long-term survival analysis of the North American intergroup study C9011 comparing fludarabine (F) and chlorambucil © in previously untreated patients with chronic lymphocytic leukemia (CLL). Blood. 2009; 114(224) Abstract 536.
11. Jelic S, Jovanovic V, Milanovic N, Marinkovic M, Kovcin V, Milosevic D, Vlajic M. Richter syndrome with emphasis on large-cell non-Hodgkin lymphoma in previously unrecognized subclinical chronic lymphocytic leukemia. Neoplasia. 1997; 44(1):63–68.
12. Mauro FR, Foa R, Giannarelli D, Cordone I, Crescenzi S, Pescarmona E, Sala R, Cerretti R, Mandelli F. Clinical characteristics and outcome of young chronic lymphocytic leukemia patients: a single institution study of 204 cases. Blood. 1999; 94(2):448–454. [PubMed: 10397712]
13. Rossi D, Cerri M, Capello D, Deambrogi C, Rossi FM, Zucchetto A, De Paoli L, Cresta F, Rasi S, Spina V, Franceshetti S, Lunghi M, Vendramin C, Bomben R, Ramponi A, Mongo G, Conconi A, Magnani C, Gattei V, Gaidano G. Biological and clinical risk factors of chronic lymphocytic leukaemia transformation to Richter syndrome. Br J Haematol. 2008; 142:202–215. [PubMed: 18492108]
14. Keating MJ, O'Brien S, Lerner S, Koller C, Beran M, Robertson LE, Freireich EJ, Estey E, Kantarjian H. Long-term follow-up of patients with chronic lymphocytic leukemia (CLL) receiving fludarabine regimens as initial therapy. Blood. 1998; 92(4):1165–1171. [PubMed: 9694704]

15. Thornton PD, Bellas C, Santon A, Shah G, Pocock C, Wotherspoon AC, Matutes E, Catovsky D. Richter's transformation of chronic lymphocytic leukemia: the possible role of fludarabine and the Epstein-Barr virus in its pathogenesis. Leuk Res. 2005; 29(4):389–395. [PubMed: 15725472]

16. Deambrogi C, Cresta S, Cerri M, Rasi S, De Paoli L, Ramponi A, Gaidano G, Rossi D. 14q32 translocations and risk of Richter transformation in chronic lymphocytic leukaemia. Br J Haematol. 2008; 144:131–133. [PubMed: 18950454]

17. Aydin S, Rossi D, Bergui L, D'Arena G, Ferero E, Bonello L, Omede P, Novero D, Morabito F, Carbone A, Gaidano G, Malavasi F, Deaglio S. CD38 gene polymorphism and chronic lymphocytic leukemia: a role in transformation to Richter syndrome? Blood. 2008; 111:5646–5653. [PubMed: 18424664]

18. Rossi D, Spina V, Cerri M, Deambrogi C, De Paoli L, Laurenti L, Maffei R, Forconi F, Bertoni F, Zucca E, Agostinelli C, Cabras A, Lucioni M, Martini M, Magni M, Deaglio S, Ladetto M, Nomdedeu JF, Besson C, Ramponi A, Canzonieri V, Paulli M, Marasca R, Larocca LM, Carbone A, Pileri SA, Gattei V, Gaidano G. Stereotyped B-cell receptor is an independent risk factor of chronic lymphocytic leukemia transformation to Richter syndrome. Clin Cancer Res. 2009; 15:4415–4422. [PubMed: 19509140]

19. Maddocks-Christianson K, Slager SL, Zent CS, Reinalda M, Call TG, Habermann TM, Bowen DA, Hoyer JD, Schwager S, Jelinek DF, Kay NE, Shanafelt TD. Risk factors for development of a second lymphoid malignancy in patients with chronic lymphocytic leukemia. Br J Haematol. 2007; 139:398–404. [PubMed: 17910629]

20. Leleu X, Soumerai J, Rocarro A, Hatjiharissi E, Hunter ZR, Manning R, Ciccarelli BT, Sacco A, Ioakimidis L, Adamia S, Moreau AS, Patterson CJ, Ghobrial IM, Treon SP. Increased incidence of transformation and myelodysplasis/acute leukemia in patients with Waldenstrom macroglobulinemia treated with nucleoside analogs. J Clin Oncol. 2008; 27:250–255. [PubMed: 19064987]

21. Robak T. Second malignancies and Richter's syndrome in patients with chronic lymphocytic leukemia. Hematology. 2004; 9(5–6):387–400. [PubMed: 15763979]

22. Robak T, Blonski JZ, Gora-Tybor J, Kasznicki M, Konopka L, Ceglarek B, Komarnicki M, Lewandowski K, Hellmann A, Moskwa A, Dmoszynska A, Sokolowska B, Dwilewicz-Trojaczek A, Tomaszewska A, Sulek K, Calbecka M. Second malignancies and Richter's syndrome in patients with chronic lymphocytic leukaemia treated with cladribine. Eur J Cancer. 2004; 40(3): 383–389. [PubMed: 14746857]

Table 1

Proportion of patients with disease transformation according to baseline characteristics

	Sample size	Richter's syndrome	Prolymphocytic leukemia	All other patients	p-value†
		(n=34)	(n=10)	(n=477)	
		No. (%)	No. (%)	No. (%)	
Treatment arm *					
F	188	14 (7)	3 (2)	171 (91)	
C	191	9 (5)	4 (2)	178 (93)	
F+C	142	11 (8)	3 (2)	128 (90)	0.78
Rai stage					
I/II	315	19 (6)	2 (1)	294 (93)	
III/IV	206	15 (7)	8 (4)	183 (89)	0.02
Gender					
Male	359	26 (7)	5 (1)	328 (91)	0.28
Female	162	8 (5)	5 (3)	149 (92)	
Mean age at study entry (in years)		62	59	63	0.55

*F=fludarabine; C=chlorambucil; F+C= fludarabine + chlorambucil

†The first p-value has 4 df; the remainder have 2 df.