

Clinical Outcomes and Prognostic Factors in Patients With Richter's Syndrome Treated With Chemotherapy or Chemoimmunotherapy With or Without Stem-Cell Transplantation

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ABSTRACT

Purpose

The purpose of this study was to assess the incidence, presenting characteristics, and treatment outcomes of Richter's syndrome (RS) and factors predicting response and survival.

Patients and Methods

An electronic database search of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) who presented at The University of Texas M.D. Anderson Cancer Center (Houston, TX) between January 1975 and June 2005 was performed, and patient medical records were reviewed.

Results

Of the 3,986 patients with CLL/SLL, 204 patients (5.1%) had possible RS, and 148 patients (3.7%) had biopsy- or fine-needle aspiration-proven RS. Treatment included chemotherapy alone and chemoimmunotherapy with rituximab. The overall response rate for the 130 assessable patients was 39% (chemotherapy, 34%; chemoimmunotherapy, 47%; $P = .2$). In multivariate analysis, factors predicting prolonged survival were Zubrod performance status 0-1 ($P = .006$), lactate dehydrogenase $\leq 1.5 \times$ the upper limit of normal ($P = .003$), platelet count $\geq 100,000$ ($P = .01$), tumor size ≤ 5 cm ($P = .02$), and fewer than two prior therapies ($P = .02$). The five adverse factors predicting shorter survival were used to design a model to predict an individual patient's risk of death: the RS score. A total of 20 patients underwent stem-cell transplantation (SCT). Patients who underwent allogeneic SCT as postremission therapy had longer survival than patients who achieved remission and received no additional therapy or patients who underwent allogeneic or autologous SCT as salvage therapy ($P = .019$).

Conclusion

A score to predict an individual patient's risk of death is proposed. Chemotherapy and rituximab combinations are effective in RS. Patients with available donors may be considered for allogeneic SCT as postremission therapy.

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INTRODUCTION

Richter's syndrome (RS), first described in 1928 by Maurice N. Richter,¹ refers to the development of high-grade non-Hodgkin's lymphoma (NHL) in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). Richter's transformation is a process that has been reported to be triggered by viral infections, such as Epstein-Barr virus infection. The large cells of RS either arise through a transformation of the original CLL clone or, less frequently, represent a new or secondary neoplasm. Genetic defects are believed

to cause CLL cells to proliferate and, by facilitating the acquisition of new genetic abnormalities, transform into RS cells.²

RS occurs in 2% to 8% of patients with CLL/SLL. The clinical outcome of the disease is generally poor. Numerous therapies can induce a response, but patients typically die within a few months after transformation to RS.

In the management of RS, it is common to use regimens that are effective in high-grade NHL or acute lymphoblastic leukemia and, in particular, agents that are non-cross-resistant and have no overlapping toxicities. In 1993, Robertson et al³

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reported our experience with 39 patients with RS. Despite multiagent therapy, the median survival duration was only 5 months.³ In 1998, we investigated the combination of fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone (Hyper-CVXD). Hyper-CVXD induced complete responses (CRs) in 38% of patients, but the median overall survival was 10 months.⁴ In recent years, important advances in the treatment of lymphoma, such as the introduction of monoclonal antibodies, have prompted us to investigate rituximab in combination with cytotoxic chemotherapy in RS. In 1999, we combined rituximab with Hyper-CVAD, and alternated this regimen with methotrexate and cytarabine plus rituximab. The overall response rate of patients with RS was 43% (CR, 27%) and the median survival duration was 9 months.⁵

Although numerous regimens have been proposed for the treatment of RS, there is no consensus on the best therapeutic approach for these patients, and clinical features that independently predict the rates of response, survival, and failure-free survival (FFS) have not been identified as they have been for aggressive⁶ and follicular lymphoma.⁷

This study summarizes our experience with patients with RS and was designed to describe the presenting characteristics, incidence, treatment outcomes, and factors predicting response, survival, and FFS in patients with RS.

PATIENTS AND METHODS

A database that includes all the untreated and treated patients with CLL/SLL who were referred to the Leukemia Service at The University of Texas M.D. Anderson Cancer Center (Houston, TX) between January 1975 and June 2005 was searched for patients with RS. All records were reviewed to determine clinical, laboratory, and pathologic features at presentation as well as disease stage, treatment, and clinical outcome. Staging evaluations at the time of presentation included complete physical examinations, bone marrow aspirations and biopsies, lymph node biopsies or fine-needle aspirations (FNA), and chest radiography or computed tomography of the chest, abdomen, and pelvis, if available. Staging and treatment were determined after review of all clinical, laboratory, and pathologic data in a multidisciplinary conference. Standard or investigational treatment was administered either at our center or in the community by collaborating physicians. The evaluation of response for all patients included in the study was performed at the M.D. Anderson Cancer Center.

Signed informed consent was obtained from all patients before all procedures and before all experimental therapy, as required by the institutional review board.

The response and end point assessments conformed to published International Workshop response criteria.⁸ CR was defined as complete disappearance of all detectable clinical and radiographic evidence of disease, disappearance of all disease-related symptoms, and normalization of biochemical abnormalities definitely assignable to RS for at least 1 month. Unconfirmed CR (CRu) included cases with minimal stable radiographic changes or with persistent lymphoid aggregates in the bone marrow without atypia. Partial remission (PR) was defined as a reduction of 50% or more in the sum of the products of the greatest diameters of bidimensionally measurable disease. Any lesser response was considered a failure. Survival was measured from the start of treatment until death from any cause or until last follow-up. FFS was defined as the time from the start of treatment until progression, relapse, or death.

The following parameters were examined in univariate and multivariate analyses for assessment of response, survival, and FFS: age, sex, presence of B symptoms, performance status, time from diagnosis of CLL/SLL to Richter's transformation, number of prior therapies (for CLL/SLL), presence of splenomegaly, presence of hepatomegaly, WBC counts, absolute lymphocyte counts,

Table 1. Incidence of Richter's Syndrome by Evidence of Transformation

Diagnosis	No. of Patients	%
CLL	3,986	100
Possible RS	204	5.1
Biopsy- or FNA-proven RS	148	3.7
Hodgkin's disease variant	13	0.3
CLL in accelerated phase	18	0.5
CLL with positive Gallium scan	11	0.3
Polymphocytic transformation	5	0.1
Other	9	0.2

Abbreviations: CLL, chronic lymphocytic leukemia; FNA, fine needle aspiration; RS, Richter's syndrome.

hemoglobin levels, platelet counts, lactate dehydrogenase (LDH) levels, beta₂-microglobulin (β₂-microglobulin) levels, albumin levels, cytogenetics, levels of immunoglobulins G, A, and M, proportion of lymphocytes and/or lymphoma cells in bone marrow biopsies, Ann Arbor stage, Rai stage,⁹ number of extranodal sites, maximum size of tumor, International Prognostic Index score,⁶ and number of disease-involved sites.⁷ The Fisher's exact test was used to assess the independence between two categorical variables. The *t* test was used to assess a difference between two groups for continuous variables. Survival curves were estimated using the Kaplan-Meier method. The two-sided log-rank test was used to test the association between variables for survival or FFS. Multivariate analysis was performed using the Cox proportional hazards regression model to determine which variables affected the duration of survival or FFS and the association between treatment and survival or FFS after adjusting for other factors. *P* values were derived from two-sided tests, and the statistical analyses were carried out using S Plus 2000 (Insightful Corp, Seattle, WA). A *P* value of less than .05 was considered significant.

RESULTS

Of the 3,986 patients with CLL/SLL, 204 patients (5.1%) had possible RS and 148 patients (3.7%) had biopsy- or FNA-proven large cell lymphoma, or RS. Thirteen patients had the Hodgkin's disease variant of RS. The remaining patients had indications of acceleration or

Table 2. Characteristics of 148 Patients With RS

Characteristic	%
Age ≥ 60 years	53
Zubrod performance status > 1	21
Hemoglobin ≥ 11 g/dL	50
Absolute lymphocyte count ≥ 5 × 10 ⁹ /L	37
Platelet count ≥ 100 × 10 ⁹ /L	57
LDH ≥ 1.5 × ULN*	47
β ₂ -microglobulin > 3 × ULN†	40
Tumor size > 5 cm	45
Time from CLL to RS > 5 years	38
IPI score	
0-2	54
3-5	46

Abbreviations: LDH, lactate dehydrogenase; ULN, upper limit of normal; CLL, chronic lymphocytic leukemia; RS, Richter's syndrome; IPI, International Prognostic Index.
*Upper limit of normal lactate dehydrogenase is 618 U/L.
†Upper limit of normal β₂-microglobulin is 2 mg/L.

Richter's Syndrome

Table 3. Response by Therapy

	All Treatments		Chemotherapy		Chemotherapy + Rituximab		Immunotherapy*	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Assessable patients	130		79		47		4	
CR	15	12	9	11	6	13	0	0
CRu	3	2	0	0	2	4	1	25
PR	33	25	18	23	14	30	1	25
NR	79	61	52	66	25	53	2	50
CR + CRu + PR	51	39	27	34	22	47	2	50

Abbreviations: CR, complete remission; CRu, unconfirmed complete remission; NR, no response; PR, partial remission.

*Three patients were treated with rituximab and one patient with alemtuzumab.

Table 4. Response, Survival, and Failure-Free Survival by Pretreatment Characteristics

	No. of Patients (N = 130)	CR + CRu + PR (%)	<i>P</i>	1-Year Survival Rate (%)	<i>P</i>	1-Year FFS Rate (%)	<i>P</i>
Age, years							
< 60	65	43	.37	38	.35	37	.14
≥ 60	65	35		37		31	
Performance status							
0-1	103	49	< .0001	44	< .0001	39	< .0001
2-4	27	4		11		12	
LDH, U/L							
< 1.5 × ULN*	67	51	.005	49	.002	44	.004
≥ 1.5 × ULN	61	26		23		21	
β ₂ -microglobulin (mg/L)							
< 3 × ULN†	68	54	.008	48	.008	44	.006
≥ 3 × ULN	45	22		27		26	
Hemoglobin, g/dL							
< 11	63	24	.0007	28	.021	26	.03
≥ 11	66	53		45		41	
Platelets, × 10 ⁹ /L							
< 100	53	19	.0001	23	.001	22	.005
≥ 100	76	53		47		42	
Albumin, g/dL							
< 3.5	50	24	.005	22	.001	18	.001
≥ 3.5	78	49		46		43	
No. of prior therapies							
0-1	63	49	.04	44	.012	42	.01
≥ 2	63	32		33		28	
Tumor size, cm							
< 5	62	48	.02	45	.011	42	.008
≥ 5	60	28		28		25	
B symptoms							
Yes	85	32	.04	29	.06	24	.04
No	41	51		50		50	
Time (CLL, RS), years							
≤ 5	79	47	.03	43	.021	37	.046
> 5	51	27		29		28	
IPI score							
0-2	71	55	< .0001	49	.002	41	.004
3-5	59	20		23		24	

Abbreviations: CR, complete remission; CRu, unconfirmed complete remission; PR, partial remission; FFS, failure-free survival; LDH, lactate dehydrogenase; ULN, upper limit of normal; CLL, chronic lymphocytic leukemia; RS, Richter's syndrome; IPI, International Prognostic Index.

*Normal lactate dehydrogenase is 618 U/L.

†Normal β₂-microglobulin is 2 mg/L.

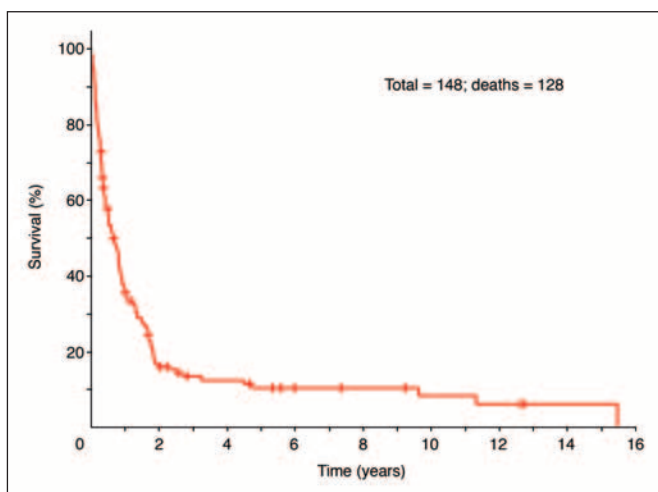


Fig 1. Survival in 148 patients with biopsy- or fine-needle aspiration-proven Richter's syndrome.

transformation, as listed in Table 1. The characteristics of patients with classical RS are listed in Table 2. The median age of the 204 patients was 61 years (range, 29 to 83 years), and 142 patients were men. Of 148 patients with classical RS, 53% were ≥ 60 years, 79% had Zubrod performance status 0 to 1, 47% had LDH levels $\geq 1.5\times$ the upper limits of normal, 57% had platelet counts $\geq 100 \times 10^9/L$, 40% had β_2 -microglobulin levels ≥ 6 mg/L, and 45% had tumors larger than 5 cm. Epstein-Barr virus was detected by in situ hybridization in the involved site of the disease in two (13%) of 15 tested patients with RS and in three (100%) of three patients with Hodgkin's disease variant.

Therapy

Of 148 patients with proven RS, 135 received therapy and 130 were assessable. Sixty-one percent of the patients received chemotherapy. Eighteen percent were treated with fludarabine or other purine analog-based therapy, 16% were treated with Hyper-CVXD and variants, 8% with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), and 19% with other therapies such as etoposide, methylprednisolone, high-dose cytarabine, and cisplatin (ESHAP) and mesna, ifosfamide, mitoxantrone, and etoposide (MINE). Thirty-six percent received chemotherapy and rituximab combination therapy: Hyper-CVXD and variants combined with rituximab (27%), fludarabine, cyclophosphamide, and rituximab (FCR; 5%), and CHOP and rituximab combination therapy (4%). Three percent of the patients received immunotherapy alone with rituximab ($n = 3$) or alemtuzumab ($n = 1$).

Table 5. Factors Independently Prognostic of Overall Survival

Risk Factors	RR	P
Performance status (0 or 1 v 2-4)	2.02	.006
Lactate dehydrogenase ($< 1.5\times$ normal v $> 1.5\times$ normal)	1.82	.003
Platelet count ($> 100 \times 10^9/L$ v $< 100 \times 10^9/L$)	1.69	.012
Tumor size (< 5 cm v > 5 cm)	1.61	.022
Prior therapies (0-1 v > 1)	1.62	.024

Abbreviation: RR, relative risk.

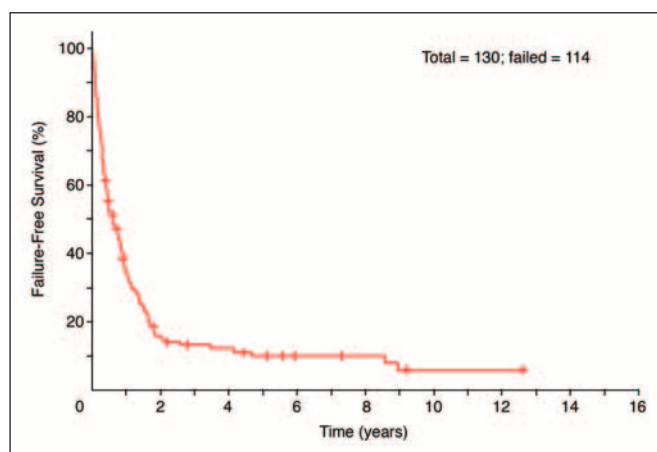


Fig 2. Failure-free survival in 130 assessable treated patients with Richter's syndrome.

Response to Therapy

Overall, 12% of patients achieved CR, 2% had a CRu, and 25% had a PR. The overall response rate was 39% (Table 3). Chemotherapy induced a response in 34% of patients, and chemotherapy with rituximab had a 47% response rate ($P = .2$). Response by pretreatment characteristics is listed in Table 4. According to multivariate analysis of the 130 treated patients, factors that independently correlated with higher response rates were platelet counts $\geq 100 \times 10^9/L$ ($P = .02$), performance status 0 to 1 ($P = .04$), hemoglobin levels higher than 11 g/dL ($P = .04$), and β_2 -microglobulin levels lower than 6 mg/L ($P = .05$). Other factors, including age, did not reach statistical significance in multivariate analysis.

Overall Survival

The median survival of all patients with biopsy- or FNA-proven RS was 8 months (95% CI, 6 to 10 months; Fig 1). In univariate analysis, pretreatment factors that correlated with shorter survival were performance status more than 1, high lactate dehydrogenase levels, high β_2 -microglobulin levels, low hemoglobin levels,

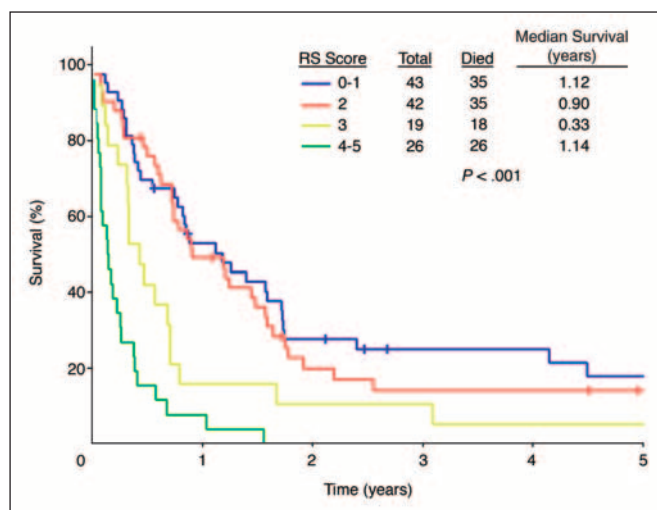


Fig 3. Survival in 130 assessable treated patients according to risk group defined by the Richter's syndrome (RS) score.

Table 6. Characteristics of 20 Patients With Richter's Syndrome Who Underwent Stem-Cell Transplantation

Patient No.	Age (years)	Sex	RS Score	Cytoreduction	Resp 1	Time From Rx to Resp 1 (months)	Time From Resp to SCT (months)	Type of SCT	SCT Source	Conditioning Regimen	Myeloablative
1	68	M	1	H-CVAD + R	CR	5.3	0.7	MUD	BM	FC + HiD R + Alemtuzumab	No
2	35	M	2	H-CVXD + R	CRu	3.1	20.5	MUD	BM	PFA	No
3	48	F	1	R + MTX + Ara-C	PD	1	8.9	MUD	BM	Flu, Melphalan	No
4	72	M	3	R + CHOP	PR	4.8	1.5	MUD	BM	FC + HiD R + Alemtuzumab	No
5	65	M	1	H-CVXD + R	PR	4.5	3.3	MUD	BM	PFA	No
6	57	F	1	R + CHOP	PR	6.3	8.9	MUD	BM	Flu, Melphalan	No
7	40	F	1	None	N/A	N/A	N/A	MUD	PBSC	Thiotepa, BuCy	Yes
8	60	M	2	H-CVXD + R	FAIL	N/A	N/A	MUD	BM	PFA	No
9	64	M	3	H-CVAD + R	FAIL	N/A	N/A	MUD	BM	PFA	No
10	54	M	4	H-CVXD + R	PR	2.4	0.4	Allo sibling	PBSC	PFA	No
11	57	M	1	FCR	PR	1.7	0.4	Allo sibling	PBSC	FC + HiD R	No
12	59	F	3	ESHAP	PR	3.1	1.1	Allo sibling	PBSC	FCR + Y-90 IT	No
13	69	M	1	CHOP	PR	5.5	8	Allo sibling	PBSC	FC + HiD R	No
14	61	F	2	H-CVAD + R	FAIL	N/A	N/A	Allo sibling	PBSC	BEAM + Alemtuzumab	No
15	63	M	3	H-CVAD + R	PR	3.7	0.6	Allo sibling	PBSC	FC + HiD R	No
16	48	F	1	R + CHOP	PR	5.6	7.2	Allo 1 Ag m*	BM	FC + HiD R	No
17	45	M	1	ESHAP	PR	2.6	3.1	Allo 2 Ag m†	BM	Thiotepa, Cy, TBI	Yes
18	60	M	1	DHAP	PR	1.1	0.9	Auto	BM	HiD Cy + TBI	Yes
19	65	F	1	PFA	CR	7.2	4.3	Auto	BM	HiD Cy + TBI	Yes
20	55	M	3	H-CVAD	PR	3.2	5.2	Auto	BM	Thiotepa, BuCy	Yes

Abbreviations: RS, Richter's syndrome; Rx, treatment; Resp 1, response to "cytoreductive" therapy; SCT, stem-cell transplantation; M, male; H-CVAD, fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; R, rituximab; CR, complete remission; CRu, unconfirmed CR; PFA, cisplatin, fludarabine, cytarabine; F, female; MTX, methotrexate; Ara-C, cytarabine; PD, progressive disease; Flu, fludarabine; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; PR, partial remission; N/A, not applicable; PBSC, peripheral blood stem cells; Bu, busulphan; Cy, cyclophosphamide; Allo, allogeneic; ESHAP, etoposide, methylprednisolone, high-dose cytosine arabinoside, and cisplatin; Y-90 IT, yttrium-90 ibritumomab tiuxetan; BEAM, carmustine, cytarabine, etoposide, and melphalan; TBI, total body irradiation; DHAP, cisplatin, high-dose Ara-C, and dexamethasone; Auto, autologous.

*Allo from a 1 Ag mismatched son.

†Allo from a 2 Ag mismatched daughter after T-cell depletion.

low platelet counts, low albumin levels, presence of B symptoms, two or more prior therapies, large tumor size, prolonged time to Richter's transformation, and high International Prognostic Index score (Table 4). In multivariate analyses of all 130 treated patients, factors that independently correlated with shorter survival were Zubrod performance status more than 1 ($P = .006$), LDH levels higher than $1.5 \times$ the upper limit of normal ($P = .003$), platelet counts less than $100 \times 10^9/L$ ($P = .011$), tumor size ≥ 5 cm ($P = .021$), and more than one prior therapy ($P = .021$; Table 5).

Failure-Free Survival

The median FFS duration of the 130 treated patients was 7 months (95% CI, 5 to 10 months; Fig 2). In univariate analysis, factors predicting shorter FFS were Zubrod performance status 0 to 1, high LDH, high β_2 -microglobulin levels, low hemoglobin levels, low platelet counts, low albumin levels, large tumor size, two or more prior therapies, presence of B symptoms, time to transformation of more than 5 years, and high International Prognostic Index score (Table 4). In the multivariate analysis of 130 treated patients, factors that independently correlated with shorter FFS were Zubrod performance status 0 to 1 ($P = .006$), high LDH levels ($P = .019$), tumor size ≥ 5 cm ($P = .021$), age ≥ 60 years ($P = .025$), more than one prior therapy ($P = .041$), and platelet counts $\leq 100 \times 10^9/L$ ($P = .045$).

Other factors, such as age, sex, B symptoms, WBC count, absolute lymphocyte count, number of cytogenetic abnormalities, Ann Arbor or Rai stage,⁹ number of extranodal sites, and bone marrow

involvement, did not reach statistical significance in univariate analysis for response, survival, or FFS.

Biopsy-Proven Versus Fine-Needle Aspiration-Proven RS

Because FNA is considered a less accurate means of diagnosing diffuse large B-cell lymphoma compared to excisional biopsy, patients diagnosed by FNA ($n = 46$) were compared with those who had biopsy-proven RS ($n = 84$). With the exception of a higher proportion of low β_2 -microglobulin levels in the biopsy-proven RS group ($P = .05$), there were no differences in the presenting characteristics and, more importantly, in the rates of response, survival, and failure-free survival between the two groups.

Independent Prognostic Factors and the Prognostic Factor Model

The sample of 130 treated patients comprised the population used to build the RS prognostic score. The five pretreatment parameters that remained independently significant in the multivariate analysis (Table 5) were used to design a model to predict an individual patient's risk of death: the RS score. Since the relative risks associated with each of the independently significant risk factors were comparable (Table 5), the relative risk of death could be characterized by summing the number of risk factors present at diagnosis. Risk groups were defined by comparing the relative risk of death in patients with each possible number of presenting risk factors (0, 1, 2, 3, 4, or 5) and

Table 7. Characteristics of 20 Patients with Richter's Syndrome Who Underwent Stem-Cell Transplantation

Patient No.	Dis at SCT	Resp 2	Progression	PFS (years)	Comments/Salvage Therapy	Survival Status	Survival From RS1 (years)	Survival From SCT (years)	Cause of Death
1	CR	CR	Yes	0.6	DHAP + R for PD 8 months after allo-SCT	Alive	1.3	0.8	N/A
2	PR*	No engraftment	N/A			Dead	2.3	0.3	Unknown
3	PD	CR	No	2		Alive	2.8	2	N/A
4	PR	PR	Yes	0.6	R + DLI for PD at 7, 8, and 10 months after allo-SCT	Alive	1.1	0.6	N/A
5	PD	PD	N/A			Dead	0.8	0.1	PD, altered mental status
6	PD	CR	No	1.2		Alive	2.2	1	N/A
7	PD	FAIL	N/A		Pre-existing Hepatitis C treated with interferon-alfa	Dead	0.1	0.1	Disseminated <i>C. albicans</i> ; NED
8	PD	PD	N/A			Dead	1.6	0.3	PD, Altered mental status
9	PD	PD	N/A			Dead	0.3	0.1	<i>Aspergillus</i> pneumonia and GI GVHD
10	PR	CR	No	5.7	PR after allo-SCT; GVHD with antitumor response, CR	Alive	6	5.8	N/A
11	PR	CR	No	4.2		Alive	4.7	4.6	N/A
12	PR	PD	N/A		R + DLI at 7 months and DLI 11 months after allo-SCT for PD	Alive	1.8	1.5	N/A
13	PD	PD	N/A		DLI at 2 months for PD; salvage H-CVAD+R at 3 months	Dead	1.8	0.7	PD, pneumonia, and GVHD
14	PD	PD	N/A		DLI	Dead	1.5	0.5	PD
15	PD	FAIL	N/A		DLI at 3 months	Dead	0.8	0.4	PD; hemorrhagic cystitis; bacteremia
16	PR	CR	Yes	1.9	Plans for R or myeloablative allo-SCT	Alive	2.6	1.5	N/A
17	PD	CR	Yes	1.6		Dead	2.7	2.2	PD
18	PR	PR	No	0.2		Dead	0.4	0.2	Liver biopsy complications; NED
19	CR	CR	Yes	7.7	FCR at relapse; breast cancer 20 months after auto-SCT	Dead	11.4	10.5	Lung infection; NED
20	PD	FAIL	N/A			Dead	0.8	0.2	Pneumonia, CNS dysfunction

Abbreviations: Dis at SCT, disease status at stem-cell transplantation; Resp 2, response to stem-cell transplantation; PFS, progression-free survival from time of stem-cell transplantation; RS1, first treatment for Richter's syndrome; SCT, stem-cell transplantation; CR, complete remission; DHAP, dexamethasone, cytarabine, and cisplatin; R, rituximab; PD, progressive disease; allo, allogeneic; N/A, non applicable; PR, partial remission; DLI, donor lymphocyte infusion; NED, no evidence of disease; GI, gastrointestinal; GVHD, graft versus host disease; H-CVAD, fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; FCR, fludarabine, cyclophosphamide, and rituximab.

*Relapsed RS 2 months prior to allogeneic SCT; patient was treated with H-CVAD+R and achieved a PR (residual disease at time of SCT).

combining categories with similar relative risks (eg, 0 with 1 or 4 with 5). Patients were then assigned to one of four risk groups on the basis of their number of presenting risk factors: 0 or 1, low risk; 2, low-intermediate risk; 3, high-intermediate risk; or 4 or 5, high risk. The survival curves and death rates over time for the four risk groups are shown in Figure 3. Patients with an RS score of 0 or 1 and 2 appear to initially have similar survival, but their survival curves separate after the first 20 months.

Stem-Cell Transplantation

A total of 20 patients underwent subsequent stem-cell transplantation (SCT). Seven patients underwent SCT as postremission

therapy, and 13 patients underwent allogeneic SCT (n = 10) or autologous SCT (n = 3) as salvage therapy. Patients' characteristics, therapies used for cytoreduction, conditioning regimens, response, and clinical outcome are listed in Tables 6 and 7.

The estimated cumulative survival at 3 years is 75% for patients who underwent allogeneic SCT after a CR, CRu, or PR, 27% for patients who responded to initial therapy and received no allogeneic SCT, and 21% for patients with relapsed or refractory RS who underwent allogeneic or autologous SCT as salvage therapy ($P = .019$; Fig 4). Survival from the time of SCT by type of transplantation and disease status are shown in Figure 5.

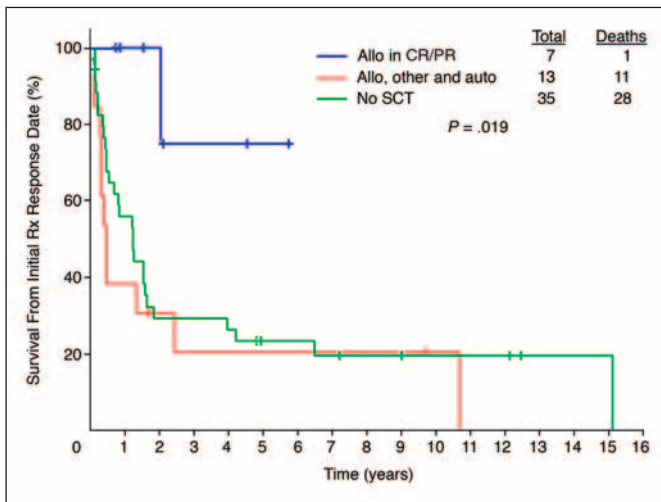


Fig 4. Survival in patients who responded to initial therapy by subsequent stem-cell transplantation (SCT). Rx, treatment; Allo, allogeneic; CR, complete remission; CRu, unconfirmed complete response; PR, partial remission; Auto, autologous.

When allogeneic SCT as a postremission therapy variable was included in the Cox proportional hazards regression model (multivariate analysis), it independently correlated with prolonged survival ($P = .002$) in the final model after a step-wise model selection procedure, but platelet count became insignificant.

DISCUSSION

In this analysis, patients with biopsy- or FNA-proven large cell transformation of CLL/SLL were assessed for treatment outcomes and factors predicting response, survival, and FFS. Combinations of rituximab with Hyper-CVXD variants or CHOP induced responses in 47% of patients compared with a 34% response rate seen with chemotherapy alone ($P = .2$). This suggests that there is a benefit from chemotherapy and rituximab combination therapies. It is notable that the

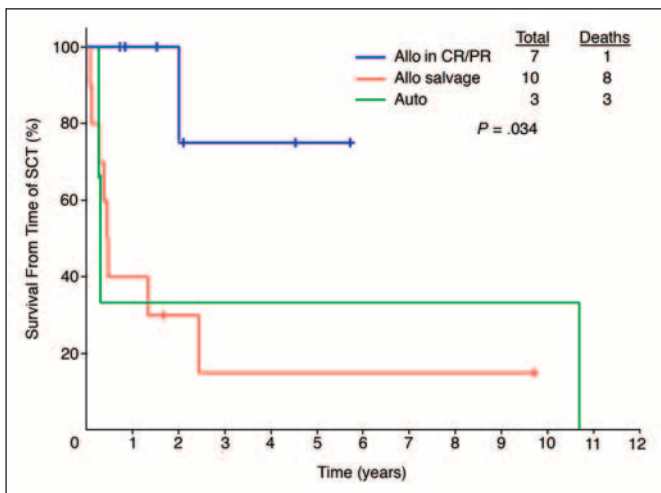


Fig 5. Survival in patients who underwent stem-cell transplantation (SCT) by type of transplant and/or disease status. Allo, allogeneic; CR, complete remission; PR, partial remission; Auto, autologous.

number of patients treated with chemotherapy and rituximab combinations compared with those treated with chemotherapy alone was relatively small. Further study with a larger sample size would be helpful to confirm our findings. In particular, 200 patients for each group are needed to achieve an 80% power at a significance level of .05.

The incidence of RS in patients with CLL was 3.7% and is within the previously reported range of 2.2% to 8%.^{3,10-15} However, only patients with biopsy- or FNA-proven RS were included in this analysis.

The superior response rates with rituximab and Hyper-CVXD or CHOP combination therapies are consistent with those attained incorporating rituximab to regimens for diffuse large B-cell lymphoma (DLBCL), such as R-CHOP (rituximab plus CHOP).¹⁶⁻¹⁹ The addition of rituximab to CHOP was shown to overcome bcl-2-mediated resistance and to prolong survival in elderly patients with DLBCL.²⁰ The Hyper-CVXD variant and rituximab combination is also very effective in mantle cell lymphoma,²¹ lymphoblastic lymphoma, and acute lymphoblastic leukemia, but have not been broadly investigated in DLBCL.

Characterization of adverse prognostic features is important in identifying patients who may benefit from specific treatment strategies. Five characteristics were identified to independently predict shorter survival: Zubrod performance status of more than 1, LDH levels higher than $1.5 \times$ the upper limit of normal, platelet counts lower than $100 \times 10^9/L$, tumor size ≥ 5 cm, and more than one prior therapy. Some of these factors, eg, poor performance status, high LDH levels,⁶ and increased tumor size,²² are similar to those independently predictive of shorter survival in non-Hodgkin's lymphoma; in addition, low platelet count and more than one prior therapy were predictive in the current analysis. The latter may reflect the development of the large cell lymphoma from cells previously refractory to therapy; a more favorable prognosis is seen in patients presenting with concurrent CLL/SLL and large cell lymphoma. In contrast, age, number of extranodal sites of disease, and stage were not significant, suggesting biologic heterogeneity between RS and aggressive non-Hodgkin's lymphoma.⁶

The RS score was developed to predict outcomes in patients with RS treated with chemotherapy with or without rituximab. The RS score may be used to identify specific risk groups and to compare different therapeutic approaches. More importantly, as patients in the high-risk group do not benefit from the above treatments, they should be considered for initial therapy with investigational agents. Allogeneic SCT appears to warrant further study. The value of additional information, such as mutational status,²³ ZAP-70,²⁴⁻²⁶ and information from genomic and proteomic analyses is unknown at the present time.

In addition, prognostic models identifying patients with CLL at risk of transforming to RS should be developed. Although some attempts have been made to predict risk factors for the development of RS in CLL/SLL,^{2,14,27} the results were either inconclusive¹⁴ or multivariate analyses were not performed.²⁷

The rates of overall survival and FFS are disappointing, with a median survival duration of 8 months and a median FFS duration of 7 months. In contrast, the outcomes of the few patients who underwent allogeneic SCT as postremission therapy were encouraging, with a 3-year estimated cumulative survival of 75% in patients who underwent allogeneic SCT as postremission therapy. However, the number of patients was

small and it is likely that some patients who underwent allogeneic SCT were carefully selected, as evidenced by the prolonged time from response to initial therapy to allogeneic SCT (Table 6). In this study, the use of relatively nontoxic, nonmyeloablative, or reduced-intensity conditioning regimens followed by donor lymphocyte infusions for progressive or relapsed disease resulted in tumor response and prolonged survival in patients with both chemosensitive and refractory or relapsed RS.

These results are consistent with a previous report from our institution showing that allogeneic bone marrow transplantation can provide a better outcome than conventional chemotherapy in patients with RS.²⁸ The results of the current study are also consistent with those we have observed with similar conditioning regi-

mens in other lymphoid malignancies.^{29,30} A critical component of these preparative regimens, for both antitumor and immunomodulatory effects, is high-dose rituximab. Given the greater sensitivity of large cell lymphoma to single-agent rituximab, the antitumor effect of rituximab may be even more pronounced in RS than in CLL/SLL.³¹

Our results demonstrate that RS should be treated with cytoreductive therapy consisting of rituximab and cytotoxic combination therapy. Patients in the high-risk group should be offered investigational approaches. Nonmyeloablative allogeneic SCT appears to be beneficial as postremission therapy in some patients, although it does not cure the majority of patients. Patients with available donors may be considered for nonmyeloablative allogeneic SCT as postremission therapy.

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Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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