

Our approach differs from a second SCT by avoiding conditioning treatment and prophylactic immunosuppression. Comparison of the results is difficult, since in most studies on second SCT, rather heterogeneous cohorts were treated. In general, TRM rates of 41–56% have been reported for second transplants following myeloablative conditioning.¹ Keeping this in mind, approaches based on immunotherapy might be preferable in terms of toxicity. Further, TRM in our study was limited to patients with an unrelated donor. Better HLA typing may improve the results of adoptive immunotherapy in the unrelated setting. So far, little is known about the role of a second SCT with nonmyeloablative conditioning, although encouraging results have been reported.⁹ However, the study population was rather small, including only seven patients with AML.

In conclusion, we feel that the use of LdAraC, MDBC, and GM-CSF is a feasible approach to the treatment of relapsed AML post allogeneic SCT. Intensive chemotherapy might not be necessary in all patients prior to adoptive immunotherapy. Patients with a longer remission post-transplant, and those who respond to LdAraC might be optimal candidates for this kind of therapy, whereas patients with early relapse may require alternative strategies. The use of GM-CSF in this setting is safe, but its clinical role remains to be defined. Relapse was the most important cause of death beyond day +100, whereas cGVHD was associated with better survival. Therefore, approaches involving further transfusions of donor cells or the use of stimulatory cytokines may improve the results, based on an ongoing GvL effect. However, a better understanding of the mechanisms responsible for GvL reactions and immune escape of malignant cells remain essentials for further improvement in the treatment of AML relapse post-transplant.

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Waldenstrom's macroglobulinemia evolving into acute lymphoblastic leukemia: a case report and a review of the literature

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TO THE EDITOR

Acute leukemia is a rare event in the natural history of Waldenstrom's macroglobulinemia, and acute lymphocytic

leukemia is even less common.^{1–8} We present a patient who developed acute lymphocytic leukemia 22 years after being diagnosed with Waldenstrom's macroglobulinemia.

This patient was an 80-year-old man, who was diagnosed with Waldenstrom's macroglobulinemia in 1979. He had been treated continuously with chlorambucil and prednisone for more than 20 years. The doses of chlorambucil varied from 2 to 6 mg/day. In May 2001, he complained of dyspnea and easy fatigability. His physical examination was unremarkable. The CBC showed white blood cell count (WBC) 6.6 K/μl, hemoglobin (HGB) 13.4 g/dl, hematocrit (HCT) 38.8% and platelet count (PLT) 159 000/μl. The serum IgM lambda monoclonal protein was 1.93 g/dl, with decreased IgG and IgA levels. The bone marrow aspirate and biopsy was consistent with Waldenstrom's

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macroglobulinemia (Figure 1). Flow cytometry showed CD5⁻, CD10⁻, CD23⁻, CD43⁻, CD20⁺, CD22⁺, FMC7⁺ B-cell population, and a reversal of kappa to lambda ratio ($\lambda/\kappa = 3.5$). The chromosomal karyotype was 46 XY. In September 2001, he underwent cystoscopy for progressive symptoms of urinary obstruction. That night, he developed gross hematuria and returned to the emergency room. His physical exam showed petechiae and his CBC was WBC 7.4 K/ μ l, HGB 11.7 g/dl, HCT 33.6% and PLT 17 000/ μ l. Review of his peripheral blood smear showed blasts. Flow cytometry results were consistent with acute lymphocytic leukemia (Table 1).

His past medical history included colon cancer diagnosed in 1977 and treated with hemicolectomy and 5-fluorouracil; localized prostate cancer Gleason (4 + 3) diagnosed in December 1998 and treated with external beam radiation; hypertension; peptic ulcer disease with subtotal gastrectomy in 1974; basal cell carcinoma resected in June 2001; cholecystectomy in 1989 and a cerebral vascular accident in 1997.

Within hours of admission, the patient abruptly developed dysarthria and left-sided weakness with rapid progression to unconsciousness. An emergent computed tomographic examination of the head showed a massive cerebral hemorrhage with herniation and hydrocephalus. The patient developed decerebrate posturing with fixed and dilated pupils. He was declared brain dead, extubated with consent of the family, and expired.

At autopsy, the bone marrow was replaced by blast cells. The spleen weighed 245 g and the liver 1415 g, both with severe lymphocytic infiltration and extramedullary hematopoiesis. The lymph nodes were normal in appearance. There was no evidence of colon or prostate cancer. Brain examination showed a large right intracerebral and intraventricular hemorrhage with falx and uncal herniation. The cerebral vasculature stained negative for congo red.

This patient died from a brain hemorrhage as a complication of secondary thrombocytopenia from Waldenstrom's macroglobulinemia, which evolved into acute lymphoblastic leukemia.

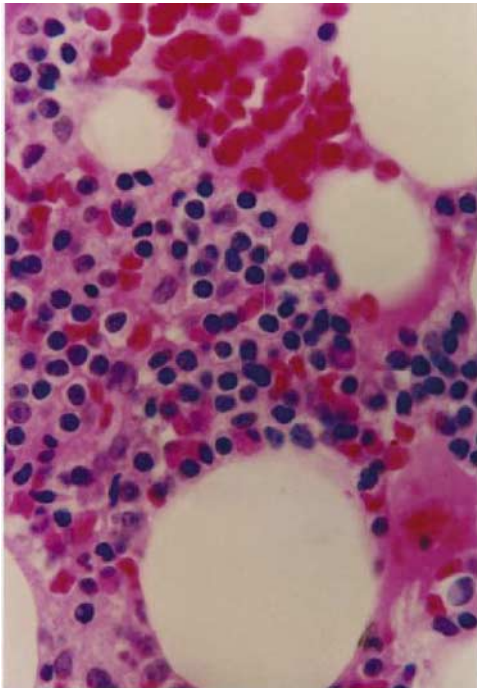


Figure 1 Bone marrow biopsy with lymphoplasmacytic aggregate.

Progression to acute leukemia is a rare event in the natural history of Waldenstrom's macroglobulinemia. A review of the literature yielded 20 cases of Waldenstrom's macroglobulinemia complicated by acute leukemia, with the vast majority of cases acute myeloid leukemia. These include patients with acute myeloblastic leukemia (8), myelomonocytic leukemia (4), erythroleukemia (4), nonlymphocytic leukemia (3) and myelodysplasia (1). One case of acute lymphocytic leukemia has been reported. The onset of leukemia ranged from 10 to 95 months after initial diagnosis of Waldenstrom's macroglobulinemia. This patient's survival for more than two decades after diagnosis is the longest interval between diagnosis and acute leukemia yet reported.

The role of exposure to alkylating agents is of interest. Eight of these patients were treated with chlorambucil, six patients were treated with melphalan, three were treated with a combination of chlorambucil and cyclophosphamide, and one was treated with cyclophosphamide alone. Two patients received no treatment at all and one patient's treatment was not documented¹⁻⁷ (Table 2). Salberg *et al*¹ reported a 68-year-old woman who was diagnosed with Waldenstrom's macroglobulinemia, but refused therapy. She developed a terminal acute monomyelocytic leukemia 4 years later. Similarly, Martelli *et al*² documented a patient who developed acute myeloblastic leukemia 10 months after diagnosis of Waldenstrom's macroglobulinemia. This patient received a total dose of 100 mg of chlorambucil.

Angelopoulos *et al* described the one case we could find where a patient with Waldenstrom's macroglobulinemia developed acute lymphoblastic leukemia. They reported a 65-year-old man who was diagnosed with Waldenstrom's macroglobulinemia in 1981, and who was treated with low-dose chlorambucil and corticosteroids until 1988. At that point, 7 years after diagnosis, the patient presented with an acute lymphoblastic leukemia and expired. Flow cytometry analysis of the blasts was positive for HLA-DR and for TdT 90%, and

Table 1 Case report flow cytometry results

	May 2001	Sept. 2001
CD5	—	—
CD7	N/A	—
CD10	—	+(77%, mod. intensity)
CD11C	+(34%)	—
CD13	—	—
CD20	+(94.1%, bright intensity)	+(23%)
CD21	+	—
CD22	+(94.8%, dim intensity)	+(94.2%, mod. intensity)
CD23	—	—
CD25	+(81.3%, dim intensity)	—
CD33	N/A	—
CD34	—	+(99%, bright intensity)
CD38	+(23.3%)	+(99.1%, mod. intensity)
CD43	—	—
CD103	—	—
CD138	N/A	—
FMC7	+(71%, mod. intensity)	—
HLADr	N/A	+(100%, bright intensity)
SigG	—	—
SigA	+(95.6%, mod. intensity)	—
SigD	+(80.4%, dim-mod. intensity)	—
SigM	+(97.3%, dim-mod. intensity)	—
sKappa	+(18.3%, mod-bright intensity)	—
sLambda	+(64.2%, mod. intensity)	—
Tdt	N/A	+(83.5%)

Table 2 Waldenstrom's macroglobulinemia associated with acute leukemia

Age	Treatment	Time to death (months)	Type of AL	Reference #
68	None	48	AML/AMMoL	1
79	Chlorambucil	10	AML	2
66	Chlorambucil	76	ANLL	3
78	Melphalan	44	AML/ery(M6)	3
68	Chlorambucil	36	AML/ery(M6)	3
71	Cyclophosphamide	54	ANLL	3
70	Chlorambucil, and cyclophosphamide	72	AML	4
85	Chlorambucil and cyclophosphamide	24	AML	4
69	Chlorambucil	24	AML	4
63	Chlorambucil	12	Myelodysplasia	5
76	(Unspecified)	95	ANLL	6
66	Melphalan	72	AML/ery(M6)	7
81	Melphalan	42	AML/ery(M6)	7
52	Melphalan	16	AML/AMMoL	7
63	Chlorambucil	54	AML/AMMoL	7
42	Chlorambucil and cyclophosphamide	60	AML	7
75	Melphalan	21	AML	7
54	Melphalan	19	AML	7
62	Chlorambucil	21	AML/AMMoL	7
65	Chlorambucil and corticosteroids	72	ALL	8

negative for CD2, CD3, CD7, CD10, CD19, CD22, CD14, CD33 and Glycophorin-A. Chromosomal analysis was not reported. This patient's course was interpreted as a possible dedifferentiation from the Waldenstrom's macroglobulinemia into a poorly differentiated ALL.⁸ The ALL, however, could have arisen from a separate clone. In our patient, the finding that immunophenotypic markers (CD22 and CD24) were present in both the acute lymphocytic leukemia cells and in the Waldenstrom's macroglobulinemia cells strengthens the concept of Waldenstrom's macroglobulinemia developing into an acute lymphocytic leukemia. The two cases together suggest that a range of ALL phenotypes may evolve from Waldenstrom's macroglobulinemia.

It is still possible that other factors in the patient's history could have contributed to the development of ALL. First, the patient's prolonged exposure to chlorambucil may have predisposed the patient to develop ALL. A number of considerations do not support this possibility. Casciato *et al* reviewed 74 cases of patients with neoplasms (solid and hematologic), who were treated with cytotoxic agents including busulfan, chlorambucil, melphalan and cyclophosphamide, and later developed acute leukemia. The median time between diagnosis and acute leukemia was 59.5 months and the median time from the beginning of chemotherapy to acute leukemia was 52 months, while the longest time interval reported was 147 months.³ Our patient had been treated for 22 years with chlorambucil and prednisone, much longer than previously reported. The majority of reports have linked chlorambucil exposure to myelodysplastic syndromes and acute myeloid leukemia.⁹ In addition, our patient had received external beam radiation 3 years previously for his prostate cancer. Acute leukemia after radiation for prostate cancer is exceedingly rare. One study of 543 prostate cancer patients treated with radiation with an average follow-up of 4 years reported only one patient with acute myeloid leukemia.¹⁰

We conclude that the acute lymphocytic leukemia in this patient was a complication of his underlying Waldenstrom's macroglobulinemia. This case indicates that Waldenstrom's macroglobulinemia patients may develop acute leukemia even in the second decade after initial diagnosis.

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