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Waldenstrom's Macroglobulinemia treated with fractionated low-dose total body irradiation

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Summary

Background: Low-dose total body irradiation (TBI) is known to be an effective treatment for low-grade non-Hodgkin's lymphoma and chronic lymphocytic leukemia but has fallen out of favor because of perceived side effects and the development of newer chemotherapy agents. The mechanism of action is poorly understood but may involve immunomodulation as well as direct cytotoxicity.

Case Report: A 78-year-old male with relapsed Waldenstrom's macroglobulinemia following therapy with chlorambucil underwent a five-week course of TBI. The total dose delivered was 1.5 Gy, given as 0.15 Gy twice weekly for ten sessions. During the course of therapy his CD4 cells increased from 637 (cells/mm³) to 808 partly through treatment and then declined to 654 at the completion of therapy. The CD4:CD8 ratio increased from 1.3 at the start to 1.7 at completion of therapy. His IgM levels declined from 4040 to 1640 following treatment and he became symptom-free. Other than transient thrombocytopenia, no acute or late side effects were noted.

Conclusions: Although rarely used now, it is important to be aware that low-dose TBI can be an effective treatment for patients with Waldenstrom's macroglobulinemia and similar conditions. The mechanism may partly be immune-mediated. Further investigation into the precise mechanism should be performed.

Key words: Waldenstrom's macroglobulinemia • total body irradiation

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BACKGROUND

Low-dose total body irradiation (TBI) was shown to be an effective therapy for patients with low-grade non-Hodgkin's lymphoma and chronic lymphocytic leukemia (CLL) many decades ago. Its use however has fallen out of favor as newer chemotherapeutics have been developed. Despite this, to date no treatment has clearly proven superior to low-dose TBI. The precise mechanism of action is uncertain but it is believed by some to be at least partly immunologically mediated.[1]. As Waldenstrom's macroglobulinemia is a neoplastic proliferation of plasma cells, it is often amenable to treatments similar to those used for low-grade non-Hodgkin's lymphoma and CLL. Here presented is a patient with Waldenstrom's macroglobulinemia who underwent a course of low-dose total body irradiation and whose CD4 cell count, CD4:CD8 ratio, and other parameters were followed during the course of radiotherapy.

CASE STUDY

In 1992 a 78-year-old retired male Naval officer underwent his routine annual physical examination. He mentioned difficulty overcoming an upper respiratory infection and the ensuing work-up led to the diagnosis of Waldenstrom's macroglobulinemia. Although his IgM levels had fluctuated between 3000 mg/dL and 4000 mg/dL, he remained well until 1997 when he began developing progressive fatigue and weakness. In January 1998 he began oral chlorambucil and prednisone. During the 6 months of treatment, he experienced nervousness and sleeplessness, but the IgM decreased from 4080 to 1605 mg/dL and serum viscosity decreased from 3.3 to 1.8. Viscosity began rising within 6 months and when it exceeded 3 and IgM exceeded 4000/mL he again became symptomatic. He refused further chemotherapy but was willing to undergo an older, infrequently utilized application of radiation therapy, fractionated low-dose total body irradiation (TBI). TBI began on September 10, 1999. The prescribed dose was 0.15 Gy given twice weekly for a total of 1.5 Gy over five weeks. The patient experienced no discomfort during the course of therapy. As shown in Table 1, IgM readings improved from 4170 to 1630 mg/dL and viscosity decreased from 3.1 to 1.7. His spleen volume decreased nearly 30%.

Because the mechanism of low dose TBI is not fully understood and is speculated to be at least partly immune-mediated,[1] relevant parameters were followed. Absolute counts of CD4 cells increased from 637 (cells/mm³) to 808 partly through treatment

and then declined to 654 at the completion of therapy. The CD4:CD8 ratio increased from 1.3 to 1.7 over the 5-week course. TBI therapy resulted in thrombocytopenia and leukopenia but counts recovered within 1-2 months. Hemoglobin was minimally affected.

Upon examination following low-dose TBI he was feeling well and energetic. With time his IgM levels rose again and in April 2001 he started fludarabine at an IgM level of 3,970 mg/dL. With 6 months of therapy his IgM declined to 1,330 mg/dL. His IgM later rose to 3,350 mg/dL and he began rituximab in January 2003 but discontinued after three infusions because of severe rigors. By June 2003, his IgM rose to 3,330 and he began a second course of fludarabine, which is ongoing. He is currently asymptomatic with regards to Waldenstrom's macroglobulinemia, but was recently bothered by signs and symptoms of congestive heart failure that are now medically controlled.

DISCUSSION

In 1944, Waldenstrom [2] reported the cases of two patients with a syndrome of anemia, mucosal bleeding, lymphadenopathy, and high serum viscosity. This constellation of signs and symptoms, now known as Waldenstrom's macroglobulinemia represents one of several clinical entities that share the common characteristic of monoclonal plasma cell proliferation and IgM hypersecretion. Other conditions in this spectrum of plasma cell neoplasms include the more common multiple myeloma as well as Castleman's disease, plasma cell leukemia, alpha-heavy chain disease and monoclonal gammopathy of unknown significance (MGUS). In Waldenstrom's macroglobulinemia the neoplastic plasma cells secrete IgM, which accounts for the elevated plasma viscosity often seen in these patients. The larger molecular size of IgM leads to hyperviscosity at lower levels than with IgG or IgA such that levels over 3 g/dl may produce symptoms including fatigue, visual disturbances, headache, shortness of breath, and mental status changes. While Waldenstrom's macroglobulinemia is often associated with lymphadenopathy and hepatosplenomegaly, it is usually not accompanied by lytic bone lesions as in multiple myeloma. Other manifestations of the disease are caused by lymphoplastic infiltrations in various tissues and may include cough and dyspnea, diarrhea and GI bleeding, exophthalmos, and cutaneous plaques or tumors. Peripheral neuropathy may develop as a consequence of IgM reactivity to myelin[3,4] or less frequently, as a result of direct infiltration by neoplastic cells.[5] Central nervous system infiltration by the malignant cells is a very rare complication known as the Bing-Neel syndrome.

Waldenstrom's macroglobulinemia is relatively rare with an incidence of approximately 1500 per year in the U.S. The etiology is uncertain but a case report of a bird breeder who developed macroglobulinemia with pulmonary involvement and reactivity of the monoclonal IgM to an antigen in canary droppings suggests that constant antigenic stimulation may play a role in pathogenesis.[6]

Treatment of Waldenstrom's macroglobulinemia typically involves alkylators such as chlorambucil with or without corticosteroids and nucleoside analogues such as cladribine and fludarabine. Objective responses are seen in the majority of previously untreated patients resulting in a mean survival of approximately 5 years.[7,8] Response rates to fludarabine as first-line therapy range from 38% to 85%.[9] Phase II trials in previously treated patients showed that fludarabine induces responses in about one third of patients who were resistant to previous treatments. Response rates to fludarabine in previously treated patients are higher for patients who are still sensitive to their primary therapy. The principal toxicity of fludarabine is myelosuppression.

An early study of 8 symptomatic Waldenstrom's macroglobulinemia patients demonstrated activity with rituximab.[10] Partial responses were noted in three patients, including two with fludarabine-refractory disease. Median progression-free survival was 6.6 months. A prospective phase II study was conducted by Dimopoulos and colleagues [11] in which 27 patients with symptomatic WM (including 15 patients who were previously untreated) were treated with rituximab 375 mg/m² for 4 weeks. Three months later, patients without evidence of progressive disease underwent a repeat 4-week course of rituximab. Twelve patients (44%) achieved a partial response. Responses occurred in 6 of 15 (40%) previously untreated patients and in 6 of 12 (50%) pretreated patients showing that both groups benefited equally. Patients with IgM levels less than 4 g/dL had higher response rates. The median time to progression for all patients was 16 months. About a quarter of the patients experienced some infusion-related toxicity, usually fever and chills.

Dimopoulos et al [12] have also observed responses to thalidomide in a prospective phase II study, although side effects were common and duration of response was short. Curiously all responding patients in this study were female. Significantly, none of the patients treated during a refractory relapse responded to thalidomide and no patients with disease duration exceeding 2 years responded.

High dose therapy with autologous and allogeneic transplantations has been used with some success.[13] In one French series, [14] autologous transplants were associated with a 95% response rate but high relapse rate. Allogeneic transplants led to 6 of 10 patients alive and progression-free at 3 to 76 months but a 40% treatment-related mortality rate. Munshi and Barlogie [15] described eight patients with WM who were treated with high-dose melphalan with autologous peripheral blood stem cell support. Adequate numbers of stem cells were collected in six patients two patients with extensive prior fludarabine therapy failed the first stem cell harvesting effort and a second attempt at collection was required. There were no treatment-related mortalities in their study. Recovery of bone marrow after transplant was prompt except in one patient with extensive prior use of fludarabine. Seven patients achieved a partial response and one experienced a complete response. The authors suggested that stem cells be procured prior to extensive use of purine analogues as this may lead to stem cell damage with decreased ability to harvest adequate numbers.

Newer approaches currently under investigation include apoptosis-modulation via oblimersen, an antisense oligonucleotide that specifically binds to the first six codons of the human bcl-2 mRNA sequence.[16] This results in degradation of bcl-2 mRNA and subsequent decrease in Bcl-2 protein translation thereby enhancing apoptosis.

A less sophisticated but sometimes effective therapy involves splenectomy. Cavanna [17] and colleagues described the case of a patient with advanced Waldenstrom's macroglobulinemia who was treated with plasmapheresis, chemotherapy, and splenic radiotherapy followed by splenectomy 14 months later for mild persistent splenomegaly and an IgM-kappa monoclonal component on serum protein electrophoresis. The histological and immunohistochemical analysis confirmed splenic involvement. At follow-up 18 years later he remained in good health and without evidence of disease. Others have also reported long-term complete remissions after splenectomy. [18,19]

Low-dose total body irradiation is a treatment that has been used for low grade lymphomas and CLL for several decades. [20,21] Consistent with its histology as a low-grade lymphoplasmacytoid lymphoma, Waldenstrom's macroglobulinemia has also been treated effectively with radiation therapy. A review of the older literature documents its efficacy but it appears to have fallen out of favor in recent years

thanks to advances in chemotherapy and immunotherapy. Despite the advances in other therapies however, none has clearly proven superior to low-dose TBI. Chaffey et al [22] found that low-dose TBI compared favorably against a historical group of chemotherapy-treated patients matched for age, sex and histology.

Phase III studies have compared low-dose TBI with various chemotherapy regimens and have not demonstrated significantly different results. In a prospective randomized trial, Hoppe et al [23] showed no significant advantage to single agent alkylating agent chemotherapy or combination chemotherapy with CVP (cyclophosphamide, vincristine, prednisone) versus total body irradiation for patients with stage III-IV favorable histology lymphomas. Brereton et al [24] found no advantage to combination chemotherapy with CVP or C-MOPP (cyclophosphamide, mechlorethamine, vincristine, procarbazine, prednisone) versus low-dose TBI combined with CVP or C-MOPP, suggesting that the addition of chemotherapy for initial treatment was of no added benefit. The British National Lymphoma Investigation Report [25] showed no significant advantage for CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) over low-dose TBI for stage III-IV intermediate grade lymphomas. In the EORTC lymphoma co-operative group trial, [26] low dose TBI plus involved field radiotherapy was compared to combination chemotherapy (CHVmP: cyclophosphamide, doxorubicin, teniposide, prednisone) plus irradiation to bulky sites. No significant difference in freedom from progression or survival was observed.

Johnson et al [27] reported low dose TBI to be as effective as CVP for stage III-IV poorly differentiated lymphocytic lymphomas in another randomized trial. Although a common fear is its toxicity, low-dose TBI was more easily tolerated than CVP. Over 50% of the 37 CVP patients developed complications which required hospitalization compared to only one of 35 TBI patients. One patient died from Candida sepsis following the first cycle of CVP. Late complications included two TBI patients who developed myeloproliferative disorders and two CVP patients who developed persistent neurologic problems.

Myelodysplastic syndromes and second malignancies, especially acute leukemias are seen in patients with low-grade lymphomas regardless of the initial treatment.[28] Travis et al [29] concluded that secondary leukemias are not uncommon following TBI, particularly if combined with alkylating agents based on the observation of 4 patients who developed acute

non-lymphocytic leukemia in a cohort of 61 lymphoma patients treated with TBI. Of note however, the median cumulative radiation dose to bone marrow in this cohort was relatively high at 5.2 Gy.

The Southwest Oncology Group investigated a unique combination of low-dose TBI with CHOP in previously untreated patients with stage III-IV diffuse non-Hodgkin's lymphoma. [30] CHOP was started on day 1 and TBI was delivered in three fractions of 0.15 Gy on days 21, 23 and 25. CHOP/TBI was repeated until four cycles of CHOP and three cycles TBI (totaling 1.35 Gy) were delivered. Although treatment was well tolerated and the authors suggested evaluating this approach in a larger cohort, this has not been further pursued.

As seen in the presented case, salvage therapy following low-dose TBI is possible. At the University of Florida, [31] 30 patients who relapsed after low-dose TBI were treated with either chemotherapy or a second course of low-dose TBI. Both salvage treatments were equally effective with 23 of the 30 patients obtaining a complete clinical response. Johnson et al [27] described 17 patients who previously received low-dose TBI and received subsequent CVP chemotherapy. Tolerance was excellent with most patients receiving full or only modestly attenuated doses. Similarly, Dobbs et al [32] reported the successful administration of chemotherapy following low-dose TBI in 31 of 37 patients. Six patients were not able to tolerate chemotherapy because of prolonged thrombocytopenia but the authors noted that these six patients had had initial bone marrow involvement.

Long-term follow-up of 68 patients treated at Rotterdamsch Radio-Therapeutisch Instituut between 1973 and 1979 showed that relapse-free survival was significantly improved in patients with low grade non-Hodgkin's lymphoma if they received low-dose TBI as initial treatment. [33] In their study, no treatment related complications were noted and subsequent chemotherapy for relapsed disease was not hampered by previous TBI. Patients relapsing after low-dose TBI received and tolerated a variety of therapies. Response rates were high, but of short duration, especially in intermediate or high-grade non-Hodgkin's lymphoma. Characteristic of the natural history of lymphomas, duration of response was progressively shorter after multiple relapses. These authors did state that the high response rates and extended RFS, without maintenance therapy, makes low-dose TBI a preferable first line treatment for patients with advanced stage low grade non-Hodgkin's lymphoma.

The presented case also illustrates that low-dose TBI can be used after chemotherapy, a finding reported by others as well.[31,32] Safwat et al [34] recently reported on 35 patients with relapsed and/or chemo-resistant NHL who were treated with low-dose TBI plus involved-field radiotherapy to bulky sites of disease. A complete remission rate of 29%, 2-years progression-free survival of 32% and a median progression-free survival of 12 months was attained. Perhaps most intriguing about this study was that, as in the presented case, low-dose TBI was associated with an increase in the CD4/CD8 ratio. In their study, low-dose TBI led to a reduction in the absolute number of all the tested cellular subsets (except CD95+ cells), but the CD4/CD8 ratio was higher than the pre-treatment ratio because the reduction in the number of CD4 positive cells (reduced by 42%) was less than the reduction of CD8+ cells (56% reduction). Interestingly, a high percentage of CD4+ cells before treatment was significantly correlated with longer response duration and overall survival. In the presented case there was actually a small increase in the CD4+ cells, which accounted for the increased CD4/CD8 ratio. Studies with mice revealed that a single dose of 0.75 Gy leads to an increase in the percentage of L3T4 (CD4+) cells from 13 to 28% while the percentage of Lyt-2 (CD8+) cells was not affected, a finding similar to what was observed in our case.[35]

These findings support the concept that low-dose TBI has an impact on the immune system, which may in part contribute to its observed clinical effect. In a study by Yonkosky et al [36] low-dose TBI resulted in enhanced *in vitro* immune response for some patients. *In vitro* proliferative responses to mitogens were 127–319% over initial values for all five patients with complete response. In contrast, mitogen responses were not improved in patients with unresponsive disease, intimating that low-dose TBI may induce immune enhancement in humans to some extent.

Other proposed mechanisms for low-dose TBI include induction of apoptosis and low-dose hypersensitivity.[37] However Safwat et al [38] recently published data that further bolsters the idea that immunomodulation plays an important role. In a mouse model of malignant melanoma, low-dose TBI augmented the efficacy of interleukin-2. The difference in tumor burden between mice following treatment with IL-2 alone versus IL-2 plus TBI was statistically significant ($p = 0.006$). This synergy is unlikely to be due in any significant degree to a direct tumoricidal effect of the low-dose TBI, given the inherent radioresistance of melanoma cells. The addition of low-dose TBI led to a significant increase in the number of natural killer cells and macrophages infiltrating the metastatic sites.

It is important to distinguish the fractionated low-dose TBI as used in the presented case from the preparative regimens commonly used as part of autologous and allogeneic transplants. In those situations the TBI dose is typically 12-15 Gy given over 4 days. "Low-dose TBI" that is used as part of non-myeloablative allogeneic transplants consists of a single 2 Gy dose, which is still much higher than in the studies mentioned above and in the presented patient.

CONCLUSIONS

Although still as effective today as it was over 35 years ago, fractionated low-dose TBI has been largely abandoned in the United States. In fact the latest editions of many widely used texts in Medical and Radiation Oncology fail to mention it at all anymore. While innovative approaches to low-grade lymphomas, CLL, and Waldenstrom's macroglobulinemia are constantly being developed, it is important not to forget other effective therapies. Perhaps a combination of one or more of these newer therapies with the older, but still useful technique of low-dose TBI will yield a true breakthrough.

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Table 1. Parameters before and during fractionated low-dose TBI

Date	IgM mg/dL	Plasma viscosity Relative to saline	PLTS x1000/mL	HgB g/dL	WBC cells per mm ³ x10 ³	T Helper percent	CD4/CD8 ratio	CD4 cells/mm ³	NK percent	WBC cells per mm ³	Spleen volume cm ³
	Normal values	46-304	1.6-1.9	150-350	13.9-19.3	4.5-11	32-68%	1.1-2.5	(0-9%)	4k to 10k	
1999 Aug 31	4170		335	11.1	7.68	43.1	1.32	637		7680	
1999 Sep 07	3870	2.9									100.4
1999 Sep 16			301	10.8	7.05	48.3	1.43	659	16	7050	
1999 Sep 23	4040	3.1	301	11.2	5.28	54.5	1.67	808	14	5280	
1999 Sep 30			199	10.8	5.45	52.67	1.62	745		5450	
1999 Oct 07			95	10.8	3.60	54.1	1.71	589		3600	
1999 Oct 11	2530	2.2	74	10.8	3.93	55.9	1.65	654	9	3930	72.4
1999 Oct 19	1770	1.9	73	11.1	2.20					2200	
1999 Oct 27			69	10.9	2.20					2200	
1999 Nov 03	1630	1.8	134	11.9	2.50					2500	