

Relapsed Non-Hodgkin Lymphoma in Fraternal Twins Managed Successfully With Rituximab Maintenance Therapy

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The incidence of non-Hodgkin lymphoma (NHL) has increased over the past few decades, making it now the fifth most common cancer in the United States. Previous studies have shown that the risk of NHL is increased with a positive family history of lymphoma.¹ We describe twins with follicular NHL who relapsed after chemotherapy and were successfully treated with rituximab and achieved long-term remission. The treatment chronology of patients 1 and 2 are shown in Figures 1 and 2, respectively.

Case Report

Case 1

A previously healthy 53-year-old female presented in November 1996 with a palpable mass on her right cheek, inside her mouth. She had a history of night sweats for 3 months, and she denied fevers or weight loss. She was referred to an oral surgeon for an excisional biopsy, which showed NHL. She then had a bone marrow biopsy. Review of the biopsies at our institution showed a discordant NHL with follicular large-cell lymphoma in the salivary gland and follicular small-cell lymphoma in the bone marrow (Figures 3 and 4). She was to be treated for the follicular large-cell NHL, the more aggressive of the 2 histologies.

The patient's past medical history included a laparotomy for a benign ovarian cyst at the age of 36 years. She was taking paroxetine (Paxil, GlaxoSmithKline) and propranolol (Inderal, Wyeth), and had been taking Premarin (Wyeth) for 2 years. She denied any tobacco or alcohol use. Her family history was significant for a twin brother diagnosed with NHL 6 months earlier (see case #2). Her parents were in good health. A maternal aunt had breast cancer at age 75. On physical examination, she had a 1-cm palpable lymph node in the left upper neck and another 1-cm node in the left axilla. A well healed scar was visible on the inside of the right cheek, with no palpable thickening or mass. The remainder of the exam was normal. Her white blood cell count was 6,100 with a normal differential, hemoglobin 10.1 g/dl, and platelets

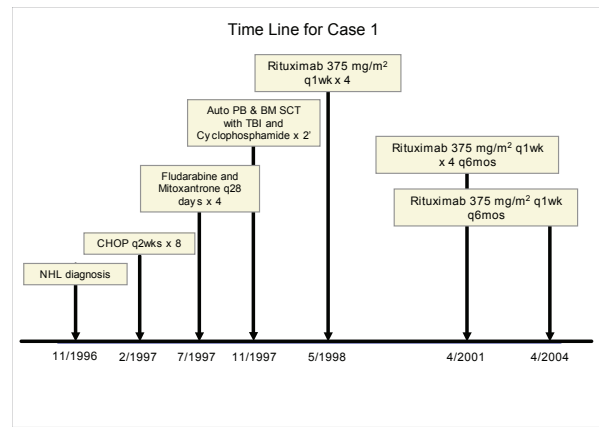


Figure 1. The relapsing course of NHL described in case 1. This patient was started on maintenance therapy in April 2001 and has remained on this in complete remission.

NHL = non-Hodgkin lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; PB = peripheral blood; BM = bone marrow; SCT = stem transplantation; TBI = total body irradiation.

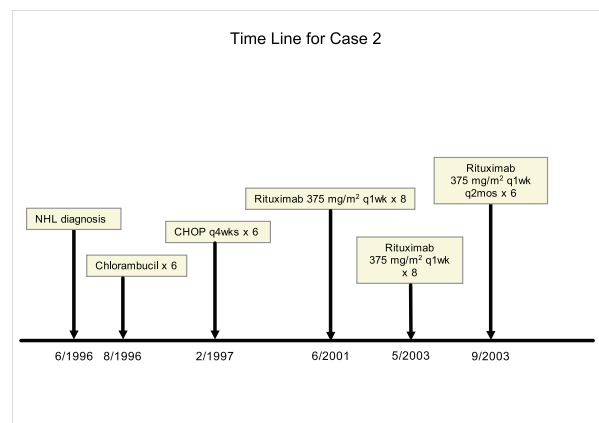


Figure 2. The course of treatment of NHL described in case 2. Of note, the patient was started and remains on maintenance therapy since May 2003.

NHL = non-Hodgkin lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone.

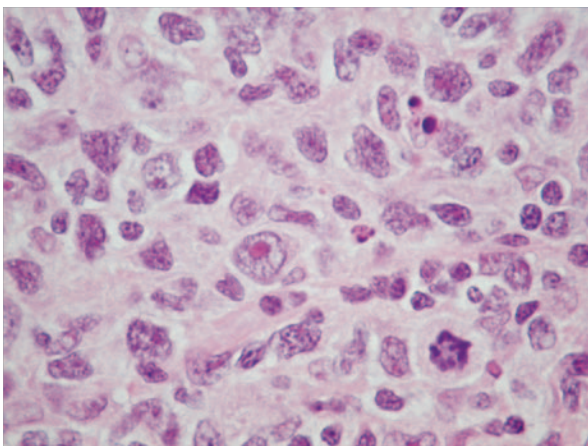
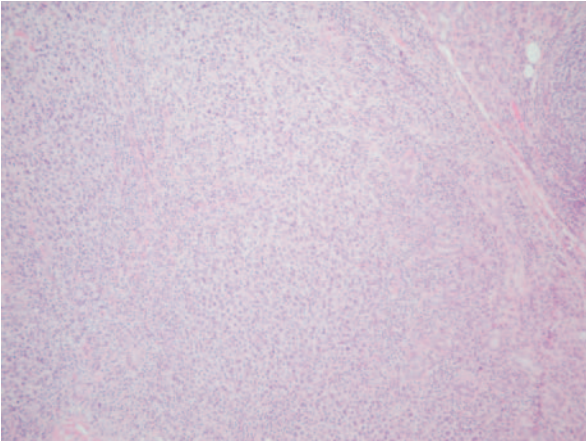


Figure 3. Photomicrograph of salivary gland biopsy of patient #1 showing follicular large-cell lymphoma under low power (upper) and high power (lower).

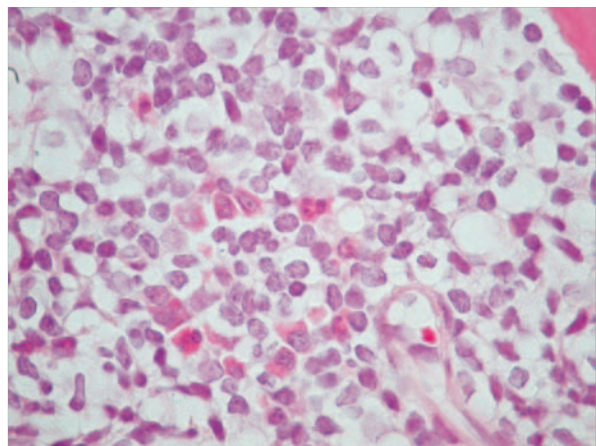
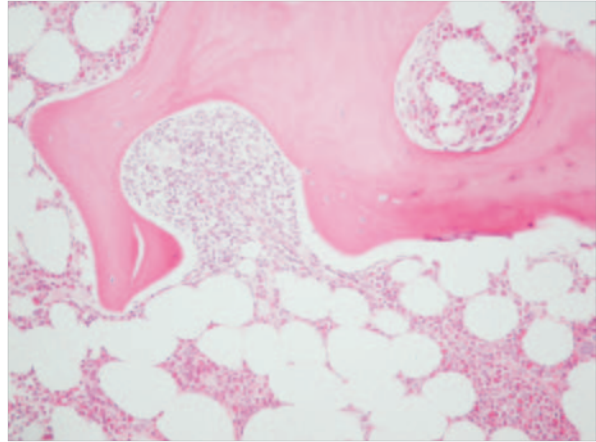


Figure 4. Photomicrograph of bone marrow biopsy of patient #1 showing paratrabecular infiltrate under low power (upper) and small-cell lymphoma (lower).

248,000. A chemistry panel showed normal renal and hepatic function, and her lactic dehydrogenase (LDH) was 198 (0–250). A computed tomography (CT) scan showed bilateral adenopathy in the neck, with a dominant lesion in the right submandibular region, and retroperitoneal and mesenteric and left inguinal lymphadenopathy (Figure 5).

The patient was initially treated on a clinical trial with biweekly CHOP (cyclophosphamide [Cytosan, Bristol-Myers Squibb], vincristine, doxorubicin [Adriamycin, Pfizer], and prednisone) with granulocyte colony-stimulating factor support for 8 cycles. Subsequent restaging showed persistent low-grade lymphoma in her bone marrow. She developed lymphadenopathy after 2 months and was treated with fludarabine and mitoxantrone. She had pain in the low back and pelvis with abnormalities in the right sacrum, right ilium, left pubis, and T5 by CT scan. She was treated with radiation therapy to a dose of 30

Gy in 15 fractions. She then underwent autologous stem cell transplantation with total body irradiation for a total of 1,200 cGy and cyclophosphamide in November 1997. Five months later she developed a palpable node in the right submandibular region. Pathology from a fine-needle aspiration of the enlarged lymph node was consistent with malignant lymphoma, CD20+, mixed cell type, predominantly small-cell type. The patient was started on rituximab (Rituxan, Genentech/Idc), 375 mg/m² intravenous weekly for 4 weeks, and achieved complete remission in June 1998. She remained in complete remission until April 2001, when she developed a mass in the right jaw and night sweats. Excisional biopsy of the jaw mass was benign, but a bone marrow biopsy showed recurrence of the low-grade, small-cell lymphoma. She was re-treated with rituximab and started on maintenance therapy (375 mg/m²) weekly for 4 weeks, every 6 months. As of April 2004, she remained in complete remission.



Figure 5. Computed tomography scan showing the patient's lymphadenopathy from case 1.

Case 2

A previously healthy 52-year-old male presented with a left thigh mass in June 1996. He had no fevers or weight loss. An excisional biopsy showed follicular small cleaved cell type NHL. A bone marrow biopsy was negative. A chemistry panel showed normal renal and hepatic function, and a CT scan did not show any enlarged nodes within the chest, abdomen, or pelvis.

The patient's past medical history included an appendectomy and an excision of a pilonidal cyst. He was taking no medications. On physical exam, subtle adenopathy was noted in the right groin. The remainder of his exam was normal, including a white blood cell count of 11,100 with normal differential, hemoglobin of 17.4 g/dL, and platelets of 190,000.

The patient was treated initially with local radiation therapy followed by oral chlorambucil. In January 1997, he developed a right anterior thigh mass, which was biopsied and identified as mixed small- and large-cell, intermediate-grade NHL. CT restaging did not reveal any additional adenopathy. It was at this time that his sister presented with NHL. He was treated with CHOP chemotherapy for 6 cycles, which was completed in June 1997. The patient developed a complete remission which lasted for 4 years. In June 2001, he noted a small nodule behind his left ear. This was biopsied and found to be follicular mixed small-cleaved and large-cell NHL, CD-20 positive. Restaging studies with a positron emission tomography (PET) scan showed 3 focal areas of uptake: the right parotid, right sternoclavicular joint, and gastrohepatic ligament. The patient was started on rituximab and received 8 weekly doses at 375 mg/m² each, which he completed in August 2001. He was also diagnosed with adenocarcinoma of the prostate in Janu-

ary 2002, which was successfully treated with radiation seed implantation therapy. In May 2003 he developed night sweats and fatigue. A CT scan showed multiple small lymph nodes in the neck, and a PET scan showed decreased uptake in the right parotid gland and no other new lesions. A bone marrow biopsy showed no evidence of lymphoma. The patient was reinduced with rituximab and started on maintenance therapy of one 375 mg/m² dose every 2 months. In April 2004, he had no evidence of disease.

Discussion

We present case histories of fraternal twins who developed follicular type NHL within 6 months of each other. Both patients had multiple relapses following treatment with conventional chemotherapy. After re-treatment with rituximab, both twins achieved durable remission.

The causes of familial clustering in NHL remain unclear. The incidence of NHL is increasing and studies suggest that this may be partially accounted for by familial predisposition as well as by environmental factors.¹ A 2-hit theory for the pathogenesis of NHL has been hypothesized.^{2,3} The first hit could be an inherited somatic mutation in a proto-oncogene or tumor suppressor gene, while the second hit may consist of environmental factors. Studying familial cases may provide insight into the etiology of NHL.

The patient in case 1 was initially started on therapy with CHOP, which, at that time, was the standard combination chemotherapy regimen for patients with aggressive NHL.⁶ CHOP cures approximately half of patients with advanced stages of diffuse large B-cell lymphoma.

Three types of monoclonal antibodies have been developed to treat lymphoma. With unconjugated monoclonal antibodies, the antibody itself mediates cell death; rituximab belongs to this class. The other 2 types of monoclonal antibodies are conjugated to either a radioisotope or a toxin. Monoclonal antibody-based therapies, either unconjugated or conjugated, offer new treatment options for patients with hematologic malignancies.⁸

Rituximab is a chimeric monoclonal antibody directed against the pan-B-cell antigen CD20. This agent induces a rapid depletion of normal CD20-positive B cells and lymphoma cells.⁹ The pivotal study that led to the regulatory approval of rituximab in relapsed or refractory indolent NHL showed response rates of 48% with standard rituximab dosing.¹⁰ Prolonged treatment with rituximab was shown to increase the event-free survival significantly, from 12 months to 23 months.¹¹ Patients who were treated with rituximab as first-line single-agent therapy for indolent NHL had response rates of 47% when reevaluated 6 weeks after therapy was initiated.

Continued maintenance therapy raised the response rates to 73%.¹²

The role of rituximab maintenance therapy is still not clearly defined. While our 2 patients were on different maintenance schedules, both of them appeared to benefit from maintenance therapy. Case 1 demonstrates that maintenance therapy with rituximab induced a 36-month remission that is continuing at the time of publication. Case 2 also remains in remission and has received ongoing maintenance therapy for 12 months. Despite the differences in scheduling, maintenance therapy appears to have been beneficial in both patients. It is still unclear if patients should continue to receive maintenance rituximab indefinitely or retreated at the time of relapse.¹³ Further studies are needed to look at this question, and evaluate the overall response rates, survival, and long-term toxicity of maintenance rituximab therapy.

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Review

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The 2 patients described by Chakravarti et al illustrate several interesting issues regarding the current management of patients with follicular NHL. The development of follicular NHL in fraternal twins is unusual; although familial cases have been described previously, they are less common than with Hodgkin lymphoma, and no specific genetic predisposition has been identified. Both patients received initial chemotherapy with standard regimens, with typical remission durations ranging from 1 year to 4 years. Of great interest in both cases is the remarkable duration of benefit derived from treatment with single-agent rituximab, even after substantial previous exposure to combination chemotherapy.

Since its introduction several years ago, rituximab has become a standard component of treatment for patients with follicular lymphoma. Although rituximab was initially approved for single-agent use in patients with relapsed/refractory indolent NHL,¹ several strategies to optimize the benefit of this agent have now been explored. Two of the major issues regarding rituximab use in the treatment of patients with follicular NHL are illustrated by the patients reported here. First, the use of rituximab plus chemotherapy combinations for first-line therapy, rather than traditional chemotherapy alone, is supported by recent clinical trials. Second, the use of scheduled retreatments with rituximab (ie, maintenance treatment) to prolong remission duration has found recent popularity.

Prior to the introduction of rituximab, a number of chemotherapy regimens had been extensively evaluated as first-line therapy. Although combination regimens produce higher response rates than single agents, and fludarabine-based combinations are slightly more active than alkylator-based regimens, the benefit of more intensive regimens versus less intensive initial therapy has not been demonstrated in randomized trials.^{2,3} In fact, treatment with combination regimens produces median remission durations of only 18–22 months, and molecular complete remissions occur in less than 20% of patients. In phase II trials, the addition of rituximab to several standard chemotherapy regimens (eg, CHOP, CVP [cyclophosphamide, vincristine, prednisone], and fludarabine) demonstrated long median progression-free survival and, when measured, high molecular complete response rates (approximately 50%).⁴⁻⁶ Preliminary reports of 2 large randomized phase III trials confirmed major prolongations of progression-free survival when rituximab

was added to either CVP or CHOP chemotherapy.^{7,8} With the addition of rituximab to CVP, progression-free survival was prolonged from 13 months to 27 months⁷; with CHOP, progression-free survival was extended from 15 months to 50 months.⁸ The relatively short follow-up of these randomized trials currently precludes any conclusions regarding overall survival benefits. However, as these trials are maturing it seems reasonable to consider first-line treatment with rituximab plus chemotherapy combinations, particularly in younger patients or those with high-risk prognostic features.

The second interesting and increasingly common use of rituximab involves prolonged, intermittent administration, with scheduled re-treatments (maintenance therapy) for patients who are responding or stable. This strategy was used in both patients described by Chakravarti et al, and in both cases resulted in prolonged remissions on rituximab therapy. In case 1, the duration of benefit from single-agent rituximab with maintenance proved to be much longer than any of this patient's previous remissions with chemotherapy. The efficacy of maintenance rituximab in prolonging duration of remission has been clearly demonstrated in several clinical trials.⁹⁻¹¹ In patients with objective response or stable disease after treatment with single-agent rituximab, maintenance rituximab doubles the duration of remission.^{9,10} Following chemotherapy with CVP, median progression-free survival was over twice as long in patients receiving maintenance rituximab versus follow-up alone.¹¹ Progression-free survival at 2 years (74% vs 58%) and 4 years (42% vs 34%; $P < .0008$) also favored the patients who received maintenance rituximab. In all reported studies, maintenance therapy with rituximab was associated with minimal toxicity.

Although maintenance treatment with rituximab has prolonged remission duration in all reported trials, several important questions remain unanswered. First, the optimum rituximab schedule and duration of maintenance therapy is unclear. Efficacy has been shown when 4-week rituximab courses are repeated every 6 months, or when 1 dose of rituximab is administered every 2 months.^{9,10} Second, the benefit of scheduled rituximab maintenance versus rituximab retreatment at the time of progression is incompletely defined. Either strategy can prolong the duration of rituximab benefit, and in a randomized phase II trial this benefit duration was similar.¹² However, the quality of life and psychological benefits of sustained remission versus a relapse/re-treatment course have not been formally assessed. Finally, the benefit of rituximab maintenance therapy following initial chemotherapy/rituximab combination therapy has not yet been assessed. With the increasing use of combination regimens, this clinical issue becomes increasingly important, and is currently being addressed in randomized trials.

The development of rituximab in the treatment of follicular NHL has provided an additional highly effective, minimally toxic treatment option. As evidenced by the case histories presented by Chakravarti et al, single-agent treatment with rituximab often results in prolonged, excellent quality remissions, allowing the patient to avoid treatment with chemotherapy for years at a time. In addition, the high level of activity noted with various chemotherapy/rituximab first-line combinations has led to increasing optimism regarding the eventual impact of these treatments on overall survival. In the course of only a few years, a huge amount has been learned about the optimum and appropriate use of this unique agent. The challenge will continue during the next decade, as multiple new targeted agents have already entered clinical development.

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(continued from page 125)

Erlotinib is also being evaluating for several other tumor types, including breast, colon, and head and neck, all of which are characterized by EGFR overexpression.

Conclusion

It is recommended to consider rapidly incorporating erlotinib into clinical practice for lung cancer. This agent can potentially be used in patients with poor performance status who may not be candidates for chemotherapy because of its associated toxicities. However, it is not yet approved for that indication as trials continue. Erlotinib is not associated with any myelosuppression, neutropenia, neuropathy, or renal failure. All NSCLC patients could ultimately be offered this agent at some point in their treatment.

Suggested Reading

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(continued from page 132) raising the question of whether it is advisable to delay therapy. However, our data suggest that in patients with initial white blood cell counts of less than 50,000, the interval between presentation to MDACC and treatment had no influence on CR rate after accounting for prognostic covariates such as age and cytogenetics. Among these patients, 25% received treatment only after 9 or more days from MDACC presentation. In most patients, an additional delay resulted from the interval between diagnosis by the referring physician and MDACC presentation. Thus, our results suggest that the risk in waiting for cytogenetic results to become available is less than the risk in giving 3+7 to patients who are either unlikely to benefit from it or more likely to benefit from intensified induction.

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