

Involved-Field Radiation Therapy as an Adjunct to the Autotransplant Preparative Regimen for Lymphoma

**David P. Schenkein, Terry Boyle, Jody Morr, David E. Wazer,
Julie Morelli, Hillard M. Lazarus, Kenneth B. Miller,
Edward Stadtmauer, Andrew Pecora, Peter Cassileth**

Department of Radiation Oncology (T.B., J. Morr, D.E.W.) and Division of Hematology-Oncology (D.P.S., J. Morelli, K.B.M.), Tupper Research Institute, New England Medical Center, Tufts University School of Medicine, Boston, Massachusetts; Ireland Cancer Center (H.M.L.), Case Western Reserve University, Cleveland, Ohio; ⁴Bone Marrow and Stem Cell Transplant Program (E.S.), University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; Hackensack University Medical Center (A.P.), Hackensack, New Jersey; Sylvester Cancer Center (P.C.), University of Miami, Miami, Florida

INTRODUCTION

Approximately 45% of adult patients with aggressive non-Hodgkin's lymphoma (NHL) will be cured of their disease with conventional chemotherapy.¹⁻³ Patients who relapse after multiagent chemotherapy have a particularly poor prognosis.⁴ A randomized prospective trial performed by the Parma group^{5,6} demonstrated a survival advantage with high-dose chemotherapy and autologous bone marrow transplantation (autoBMT) for patients in sensitive relapse compared with a conventional salvage regimen. Although both arms in the Parma trial received involved-field radiation therapy (IFRT), its importance to the overall treatment remains unclear.⁶

The rationale for the use of IFRT is supported both by the recently completed Eastern Cooperative Oncology Group (ECOG) and Southwest Oncology Group (SWOG) trials^{7,8} and by the pattern of relapse observed by other investigators.⁴ However, contemporary practice for the use of radiation therapy in combination with high-dose therapy largely reflects institutional preferences. Neither the appropriate fields nor the appropriate sequencing of radiation in conjunction with bone marrow transplantation has been adequately defined.

This study reviews current published data on the role of IFRT as an adjunct to autologous transplantation and reports on the impact and toxicity of IFRT in combination with high-dose sequential (HDS) chemotherapy. Schenkein et al.² (and Boyle T, Morr J, Wazer D, et al., unpublished data), have reported on the feasibility and efficacy of this treatment approach in newly diagnosed high-risk patients with NHL.

PATIENTS AND MATERIALS

Patient Characteristics

Between October 1993 and October 1996, 31 patients were treated according to a prospective phase 2 protocol at 5 participating centers.² HDS chemotherapy consisted of intensive, non-cross-resistant agents delivered in 5 sequential treatment phases, followed by autologous peripheral blood stem cell transplantation (PBSCT) as initially described by Gianni⁹ and revised by Schenkein.²

IFRT was used in 15 of the 27 patients (56%) following transplantation (Boyle T, Morr J, Wazer D, et al., unpublished data). Radiotherapy was initiated at a median of 61 days (range, 31–136 days) following stem cell infusion. IFRT was delivered to 2 patients achieving complete remission (CR), 10 patients achieving partial remission (PR), and 3 patients with persistent disease. Radiotherapy was delivered to a median of 3 sites (range, 1–6 sites) as defined by the Ann Arbor Staging Manual. Patients received a median of 2400 cGy per site (range, 1980–5400 cGy). Twelve patients did not receive IFRT because of early progressive disease following transplant ($n = 2$), no areas of bulky disease ($n = 5$), early complications ($n = 2$), and unknown reasons ($n = 3$). Toxicity resulting from radiotherapy was determined from medical chart review and graded according to the ECOG system.

RESULTS

The median follow-up for the cohort was 26 months (range, 2–59 months) after the infusion of stem cells. The overall and relapse-free survival (OS and RFS) rates were 63% and 56%, respectively. OS was 73% and 50% ($P=.13$) with and without the use of IFRT, respectively (Boyle T, Morr J, Wazer D, et al., unpublished data). Relapse occurred in 12 of 27 patients (44%). Two of the patients who suffered late relapses are currently disease-free after undergoing either a second transplant or further multiagent chemotherapy. RFS was 73% for the IFRT group vs. 33% for the group that did not receive IFRT ($P=.03$) at a median follow-up of 26 months.

Patterns of Failure

Local failure following IFRT occurred in 4 of 15 patients (27%). Failure in the radiation portal occurred in all 3 patients considered to have radiographic persistent disease following HDS chemotherapy. The mean radiation dose in the group of patients with in-field failure was 2434 cGy (range, 2400–4580 cGy), and radiotherapy was initiated within an average of 67 days (range, 42–93 days) from PBSC infusion. The mean radiation dose for the patients without evidence of failure was 2929 cGy (range, 2000–5400 cGy), and radiation therapy was initiated

within an average of 58 days (range, 31–105 days) from PBSC infusion. These differences did not reach statistical significance.

Toxicity

Toxic effects occurred in 10 patients receiving IFRT following HDS chemotherapy and PBSCT (Boyle T, Morr J, Wazer D, et al., unpublished data). Grade III toxicity (hematologic) occurred in 3 patients. These patients required a significant break in the course of their radiation treatments (14–15 days) because of myelosuppression, required transfusions, and hematologic growth factors. There were no grade IV or V toxicities. Esophagitis was the most common form of toxicity recorded; however, all cases were minor grade I symptoms.

DISCUSSION

The use of IFRT is supported historically by the fact that 70%–80% of patients with stage I NHL who are disease negative, documented by laparotomy, achieve prolonged survival with radiation alone.^{10,11} Using 4 cycles of ProMACE-MOPP (cyclophosphamide, etoposide, doxorubicin, nitrogen mustard, procarbazine, vincristine, and high-dose methotrexate) with 4000 cGy IFRT, Longo et al.¹⁰ reported durable remissions in 96% of early-stage intermediate and high-grade NHL. Philip et al.,⁴ in their analysis of 100 patients with advanced NHL who failed conventional therapy and then went on to high-dose therapy, reported that 67% of the episodes of progression were isolated and involved initial sites of disease. It was their conclusion that local control remained a major factor. A program of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) for 4 cycles and IFRT to 4000–4400 cGy and 3600 cGy to proximal uninvolved nodal regions¹² yielded a local recurrence rate of 3.3% in 183 patients with early-stage aggressive NHL. The ECOG reported the results of a randomized trial involving 345 patients with intermediate early-stage NHL.⁷ In that trial, patients received 8 cycles of CHOP and then were randomized to 3000 cGy to sites of pretreatment involvement vs. no further treatment. At 6 years, improved DFS was reported for the radiation therapy arm, 73% vs. 58% ($P=.03$), and OS was better in the radiation therapy arm, 84% vs. 70% ($P=.06$). Of interest in this trial is that 28% of PRs were converted to CRs with additional radiation therapy. The SWOG⁸ completed a similar study but used short-course CHOP plus 4000 cGy vs. CHOP alone. Estimates of survival at 4 years favored the radiation therapy arm, 87% vs. 75% ($P=.01$).

The updated LNH87-2 trial,¹³ which compared sequential chemotherapy versus autologous transplantation as consolidation for NHL patients in first complete remission, reported superior DFS (59% vs. 39%) and OS (65% vs. 52%) for 236 high-risk patients. Haioun et al.¹³ did not report radiation as part of either the

preparative or consolidative phase of treatment. The Parma data⁵ demonstrated a 53% OS at 5 years with autologous transplantation for patients with chemotherapy-sensitive NHL in relapse. Forty-five percent of the patients received 130 cGy bid to a total dose of 2600 cGy to areas of bulky disease as part of the preparative regimen. There was a nonsignificant RFS advantage for the group receiving radiation therapy, compared with the group that did not receive radiation therapy, 64% vs. 45%, respectively.

Numerous authors have observed that transplant failures result from progressive lymphoma rather than toxicity. Phillips et al.¹⁴ reported on a group of 68 patients with relapsed NHL treated with intensive chemotherapy, TBI, and autologous marrow transplantation. In their study, when disease could be covered with a conventional radiation port, it was treated with 2000 cGy IFRT. They reported a trend toward improved survival with the use of IFRT ($P=.07$) before transplant.¹⁴ Mundt et al.¹⁵ reported on the use of IFRT in a group of 53 patients with aggressive NHL treated with high-dose chemotherapy and PBSCT. They reported a 61% local control rate for sites amenable to a radiation port but not irradiated. Local control for sites failing to achieve a CR was 29%; of note, adjuvant IFRT improved the local control to 100% ($P=.05$). A 2-year event-free survival of 70%, reflecting the use of IFRT posttransplant, was reported by Brasacchio et al.¹⁶ vs. 35% without IFRT. Advantages of IFRT for progressive Hodgkin's disease have been reported by several authors.¹⁷⁻²⁰ Phillips et al.¹⁷ reported a trend toward increased OS ($P=.09$) with the use of IFRT. Mundt et al.¹⁸ noted that patients with refractory Hodgkin's disease with persistent disease posttransplant had a better RFS of 40% vs. 12% ($P=.04$) with the use of IFRT. Similar observations have been made by Horning et al.,¹⁹ who reported an improved 3-year RFS of 100% vs. 60% ($P=.04$) with the use of IFRT posttransplant. Pezner et al.²⁰ described a 7% in-field failure rate posttransplant for sites treated with IFRT.

The issue of dose is more complex, however. Mauch²¹ currently recommends 4000 cGy for patients with diffuse large cell lymphoma who achieve a CR to multiagent chemotherapy. In the present study (Boyle T, Morr J, Wazer D, et al., unpublished data), there was a 27% in-field failure rate at a dose of 2400 cGy. The mean radiation dose for patients without failure in the radiation portal was higher, 2935 cGy vs. 2455 cGy.

Several studies have documented the higher toxicity of IFRT when used before radiotherapy, particularly in patients receiving thoracic radiation.²² In addition, the use of radiotherapy within the preparative regimen has the potential to increase the risk of secondary malignancies, in particular, MDS and acute leukemia.²³

Vose et al.²⁴ have recently analyzed data from the Autologous Blood and Marrow Transplant Registry (ABMTR) on the use of autologous transplantation for 184 patients with aggressive NHL that had never achieved a remission to standard chemotherapy. In multivariate analysis, not receiving posttransplant IFRT

was an adverse prognostic factor ($P=.05$). Other adverse factors included chemotherapy resistance, receiving >3 prior chemotherapy regimens, Karnofsky score <80% at transplant, and age >55 years. In contrast, registry data from the ABMTR have failed to demonstrate an advantage for IFRT with transplant in patients in first relapse or second complete remission (Lazarus, HM, personal communication).

Overall, the data from nonrandomized clinical trials suggest that IFRT posttransplant is well tolerated and likely decreases field relapses at sites of prior disease. However, randomized prospective clinical trials will be needed to fully answer this question.

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