

Phase II study of Dose-Reduced Consolidation Radiation Therapy in Patients with Diffuse Large B-cell
Lymphoma

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1.0 BACKGROUND AND SIGNIFICANCE

1.1 Chemotherapy and Radiation Therapy for Diffuse Large B-Cell Lymphoma

Based on two randomized studies performed in the 1980s and 1990s (1, 2), chemotherapy followed by involved-field radiation therapy has become a standard treatment for patients with early-stage diffuse large B-cell lymphoma (DLBCL). In these studies, chemotherapy consisted of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Radiation therapy (RT) consisted of 30 Gy in the ECOG study (1) after eight cycles of CHOP and 40-55 Gy in the SWOG study (2) after 3 cycles of CHOP. Our practice at Duke, which is consistent with guidelines set forth by the National Comprehensive Cancer Network, is to treat patients who achieve a complete response after 4 to 6 cycles of chemotherapy with radiation therapy, 30 Gy, to originally involved sites.

Chemotherapy is the cornerstone of treatment for patients with stage III-IV DLBCL, and the role of consolidation RT is not well defined. Retrospective studies evaluating the role of RT are conflicting (3, 4). The only randomized phase III trial is the one carried out by Aviles et al. This study demonstrated improved event-free survival and overall survival for patients with stage IV DLBCL who received radiation therapy to original sites of bulky disease after achieving a complete response to chemotherapy (5). Currently, we do consolidate with radiation therapy selected patients with advanced DLBCL with radiation therapy who achieve CR with chemotherapy. These patients are generally treated to all sites of original disease if practical (as opposed to just bulky sites).

While CHOP is the most common regimen used for DLBCL, other regimens have been found to be equally effective (6). At Duke, the vast majority of patients are treated with rituximab and CHOP (R-CHOP), though other regimens are occasionally employed based on medical comorbidities and side effect profile.

1.2 Rituximab for DLBCL

Since the initial studies of radiation therapy in early stage DLBCL were performed, the standard therapy for DLBCL has been significantly improved with the addition of rituximab to the standard CHOP regimen. Several randomized studies have evaluated CHOP versus R-CHOP showing a significant improvement in both progression-free survival and overall survival with the addition of rituximab (7, 8). As a result of more effective chemotherapy regimens, a lower dose of consolidation radiation therapy than has previously been studied may be effective.

1.3 PET Assessment after Chemotherapy

Positron emission tomography (PET) scans have become standard in lymphoma management to both assess disease extent at diagnosis as well as evaluate response to therapy. Patients treated with chemotherapy alone who have not achieved a complete response by PET are at substantially higher risk of relapse compared with patients who have a negative post-chemotherapy PET(9-11). A positive PET is also associated with an increased risk of local failure after chemotherapy and consolidation RT. In a study from Duke, patients with a positive post-chemotherapy PET were at higher risk of in-field failure compared with patients with a negative post-chemotherapy PET after administration of consolidation RT(12). Four-year in-field control was 97% with a negative PET versus 81% with a positive PET ($p<0.01$). The median RT dose was 30 Gy. Thus, PET scans help discriminate patients who have not had an optimal response to chemotherapy and are at increased incidence of disease relapse after a combined modality regimen. These patients may require a higher dose of consolidation radiation therapy and would not be candidates for this study. PET interpretations be standardized based on the Deauville Criteria. In the setting of combined modality therapy, a Deauville score of 1-3 is currently considered negative and a Deauville score of 4-5 is currently considered positive.

1.4 Risk of In-field Failure after Combined Modality Therapy

In-field failure (disease recurrence within the radiation field) is rare after combined modality therapy. In three large randomized trials, crude in-field failure rates after CHOP and radiation therapy (30 to 40 Gy) ranged between 4% and 7% (1, 13, 14). In these studies, rituximab was not administered and PET scans were not used to assess response to chemotherapy prior to consolidation RT.

1.5 Rationale for Radiation Therapy Dose Reduction

There are no prospective studies in DLBCL guiding the appropriate dose that should be used after effective chemotherapy. In Hodgkins lymphoma, the German Hodgkin Study Group HD10 recently demonstrated that 20 Gy was as effective as 30 Gy after 2-4 cycles of ABVD in patients with early-stage, favorable disease (ASH 2009). The risk of complications related to radiation therapy, including cardiac disease and secondary cancers, appear to be related to both dose (15) and volume (15, 16). If the dose and volume of radiation therapy can be reduced, while maintaining high rates of disease control, this would undoubtedly decrease the risk of side effects and long-term risks.

1.6 Rationale for Radiation Therapy Field Reduction

There is no consensus as to the optimal RT field size for patients with DLBCL. Many institutions follow the pattern used for Hodgkins lymphoma, namely treating an involved field (i.e., a region as opposed to true anatomic extent of disease) (17). However, several cooperative groups and institutions currently treat only originally involved sites (as opposed to regions). For example, in a retrospective analysis from the University of British Columbia of patients treated with combined modality therapy for DLBCL (3 cycles of CHOP +/- rituximab), the local control rate was equivalent between involved field and involved node treatment volumes (18). Only 2% of patients developed a marginal recurrence, defined as a recurrence outside the involved nodal field but within what would have been encompassed with an involved field. The same group has recently reported similar findings for Hodgkin's Disease (19). In this study, we will treat the original anatomical extent of disease and not attempt to treat sites which were not clinically involved at diagnosis. The hypothesis being, that chemotherapy can successfully eradicate microscopic disease, and consolidation RT will be utilized to help control gross disease.

2.0 PURPOSE

This phase II study will evaluate whether a reduction in the RT dose, concomitant with a decrease in the RT field size, in patients that achieve CR and have a negative post-chemotherapy PET scan following 4 to 6 cycles of rituximab containing chemotherapy, will be associated with a low risk of in-field failure. The goal of this approach is to maintain excellent control rates while minimizing the risk of acute and late toxicity.

2.1 Hypothesis

Hypothesis- After more effective systemic therapy (employing rituximab), with confirmation of optimal response to chemotherapy (Deauville score of 1-3 on post-chemotherapy (or interim) PET scan), the RT dose and treatment volume can be safely reduced from 30 Gy to 20 Gy while maintaining high rates of local control.

3.0 OBJECTIVES

3.1 Primary Objective

To determine if high rates of local control can be maintained after a reduction in the RT dose and volume after 4 to 6 cycles of rituximab containing chemotherapy.

3.2 Secondary Objectives

3.2.1 To determine the progression-free survival and overall survival after chemotherapy and low-dose (20 Gy) consolidation radiation therapy.

3.2.2 To identify patterns of failure after low-dose, reduced volume consolidation radiation therapy.

4.0 PATIENT RECRUITMENT

This is a prospective, phase II, single arm study. Ascertainment of eligibility will be determined by review of the records of patients with DLBCL seen by radiation oncology PI, co-investigator or other clinical faculty of radiation oncology. The subject population (with no gender or minority restrictions) will include adult patients meeting the eligibility criteria. Inclusion of women and minorities is encouraged. All patients must sign an IRB-approved informed consent prior to enrollment. Eligibility of patients will be ascertained by reviewing necessary portions of the medical record.

5.0 PATIENT SELECTION

5.1 Eligibility

1. Histologic documentation of diffuse large B-cell lymphoma, or any of its variants as defined in the WHO classification, including but not limited to any of the following:
 - a. DLBCL NOS
 - b. Primary mediastinal DLBCL
 - c. T cell/histiocyte-rich large B-cell lymphoma
2. Completion of at least 4 cycles of a rituximab-containing, anthracycline-based combination chemotherapy regimen no sooner than 3 weeks and no longer than 8 weeks prior to the start of radiation therapy
3. Deauville score of 1-3 on post-chemotherapy (or interim) PET scan
4. ANC \geq 1000 and platelet count \geq 40,000
5. \geq 18 years of age.
6. For females of childbearing potential, a serum pregnancy test within 2 weeks prior to registration; Note: if pelvic irradiation is to be given, the serum pregnancy test must be repeated within 48 hours prior to registration.
7. Signed study-specific informed consent.
8. For patients with HIV/AIDS, the following must be true:
 - The patient is compliant on combination anti-retroviral therapy (CART)
 - The patient has CD4 count \geq 200 at time of diagnosis

5.2 Ineligibility

1. Any contraindications to irradiation.
2. Primary CNS lymphoma

6.0 PRETREATMENT EVALUATION

1. A complete history and physical within 4 weeks of consent
2. Routine laboratory work including complete blood count (CBC) at least 3 weeks after chemotherapy and less than 4 weeks before beginning radiation therapy.
3. PET/CT (interim or post-chemotherapy), available for review
4. Negative serum pregnancy test for women of child-bearing potential

7.0 REGISTRATION PROCEDURE

The patients will be recruited from the clinics by the radiation oncologist from his/her practice. Only radiation oncologists listed as Key Personnel for this study and who have completed the required ethics training may enroll patients on this study. The patient's primary medical oncologist will be apprised of the patient's intent to participate in the study. Following verification of eligibility the patient will be assigned a sequential study ID number.

8.0 TREATMENT

8.1 Radiation Therapy

Radiation therapy is to be initiated no sooner than 3 weeks after completion of chemotherapy. It is strongly recommended that radiation therapy start within 8 weeks of the final cycle of chemotherapy.

Equipment

All patients will be treated using conventional or three-dimensional techniques (preferred) or intensity-modulated radiation therapy via a linear accelerator using photon energies of 6 and/or 15 MV.

Treatment Planning

An immobilization device, such as a styrofoam mold or thermoplastic head mask, will be designed for each patient. Intravenous and oral contrast will be administered if necessary to optimally design the radiation fields in the absence of medical contraindications, such as an allergy to iodinated contrast.

Target Volume

Stage I-II disease- The clinical target volume (CTV) will include the original extent of disease plus a margin of 0-5 cm to account for uncertainties in defining this volume in the post-chemotherapy setting. Within the lung and abdomen, the pre-chemotherapy length but the post-chemotherapy width will be contoured as target (to protect critical structures such as lung and kidney). The CTV will be expanded by 5-10 mm to account for daily set-up error and/or target motion (such as the respiratory-induced movement of the hilum). The PTV will be expanded by 5-8 mm to account for beam penumbra when three-dimensional techniques are utilized.

Stage III-IV- Treatment volumes for patients with advanced DLBCL will be individualized based on the clinical presentation. When feasible, consolidation of all sites originally involved is encouraged. However, consolidation of only certain sites (such as sites of bulky disease) will be acceptable.

Treatment

Patients will be set up daily using on-board imaging or weekly/biweekly MV portal films. Radiation will be given with 5 fractions per week. Patients will be treated with 1.5 to 2 Gy fractions to a total dose of 18 to 20 Gy. Treatment to subportions of the target volume can be reduced if critical normal structures are in close proximity (i.e. limiting the dose to 18 Gy to the kidneys).

Treatment Interruptions during RT

Treatment breaks due to RT-induced toxicity are expected to be rare. To be eligible for study participation, subjects must have a baseline ANC ≥ 1000 . It is very rare for patients who initiate radiation therapy with an ANC > 800 to become neutropenic during the course of treatment. The standard of care for lymphoma patients receiving chemotherapy is to continue all cycles of chemotherapy despite episodes of neutropenia unless the patients experiences an episode of febrile neutropenia (temperature greater than 100.5 degrees with an ANC ≤ 500). This study will follow the

medical oncology model and radiation treatment will continue during episodes of neutropenia, unless febrile neutropenia occurs. However, treatment breaks will be provided for thrombocytopenia, which is defined as platelets < 25,000.

9.0 EVALUATIONS DURING AND AFTER TREATMENT

9.1 During Radiation Therapy

1. All patients will be evaluated by a radiation oncologist weekly during RT or more frequently as indicated.
2. An interim history and directed physical examination will be performed during the weekly treatment check with documentation of treatment-related acute toxicity
3. A CBC will be obtained during the course of radiation treatment.

9.2 Criteria for Going off Protocol

1. Non compliance with protocol requirements.
2. Patient request or withdrawal of consent.

9.3 Follow-up

Patients will be encouraged to return every 6 months for the first two years to Radiation Oncology and annually thereafter for follow-up. The medical oncologist will also evaluate the patient routinely per standard evaluation practices. This usually involves a CT or PET/CT every 6 months for 2 years following the completion of radiation treatment. All follow-up examinations, including laboratory work and imaging studies will be performed at the discretion of the treating physicians. However, if a patient relapses, either CT or PET imaging is highly recommended to ascertain sites of disease recurrence in relation to the radiation treatment fields.

9.4 Adverse Event Capture

Adverse event information will be collected for up to five years following completion of study treatment. Only adverse events that are related, probably related, or possibly related to study treatment will be captured.

10.0 CONFIDENTIALITY and PROTECTION of RESEARCH SUBJECTS

All study-related materials will be stored electronically on password-protected DUHS maintained servers. All personnel involved in the conduct and analysis of data from the study will have ethics training in the protection of research subjects.

11.0 PROTOCOL MANAGEMENT and DATA COLLECTION

This study will be conducted in accordance with applicable Federal regulations and radiation therapy standards. Data will be entered in the study specific database within a timely manner.

12.0 RISKS/BENEFIT ASSESSMENT

Radiation therapy is a standard treatment modality for patients with DLBCL. The risks of treatment are expected to be less since a lower dose of RT will be employed. It is possible that 20 Gy is insufficient which may increase the risk of disease recurrence which may necessitate further treatment. With smaller RT doses, it is expected that both acute and long-term toxicity will be less.

13.0 COSTS

Since chemotherapy and radiation therapy are standard of care for DLBCL, all costs of the treatment as well as follow-up examinations will be billed to the patient or their insurance carrier.

14.0 STATISTICAL CONSIDERATIONS

Statistical Analysis of Primary Objective

This trial will accrue 62 patients over a time period of approximately 5-6 years. The primary objective is to determine whether the *observed* 5-year LC rate, estimated from the Kaplan-Meier curve of time-to-local failure, is as high as that observed in historical controls, i.e., 0.90. Time -to-local-failure is defined as time from on-study to time of local failure; deaths are censored; distant failures are ignored (i.e., we will continue to follow for local failure after observing a distant failure). The lower 90% confidence bound of the 5-year LC rate will be calculated, and if the lower 90% bound is ≥ 0.84 , the study will be considered a success. This decision rule is equivalent to requiring that the observed 5-year LC rate be ≥ 0.90 . If the true 5-year LC rate is 0.84 (0.94), there is 7% (87%) probability that the lower bound will be ≥ 0.84 . These probabilities (7% and 87%) are the alpha (one-sided) and power, respectively, for the null hypothesis that the 5-year LC rate is ≤ 0.84 and the alternative hypothesis that the 5-year LC rate is ≥ 0.94 . The expected number of events in this study assuming each of these distributions is 15.0 and 5.4, respectively.

The operating characteristics of the design above take into account two interim analyses designed to stop the study early when there is evidence that the null hypothesis is true. The first analysis will be done after 45 person-years (PY) of follow-up have accumulated (at about year 3). We will also perform a second interim analysis if the trial is accruing slower than anticipated, after 185 person-years of follow-up. These interim analyses will assess whether the cumulative incidence of LC (i.e., the number of events divided by the total PY of follow-up) exceeds the values shown in the table below. If the cumulative incidence is “too high,” the trial will stop. The probabilities of stopping early are also shown in the table.

Stage	Analysis time	Minimum cumulative incidence needed to stop the trial and accept the null	Probability of accepting the null when the null is true (when the alternative is true)
1	~3 years (45 PY)	0.044 (2/45)	0.35 (0.06)
2	~6 years (185 PY)	0.032 (6/185)	0.32 (0.01)
3 (Final)	11 years	NA	0.26 (0.05)

Statistical Analysis of Secondary Objective 1

Progression-free survival (PFS) will be defined as the time from on-study to disease progression or death due to any cause, whichever comes first. Overall survival will be defined as the time from on-study to death due to any cause. Both distributions will be estimated with the Kaplan-Meier method. The 5-year PFS rate and the 5-year overall survival rate will be given with their 80% confidence intervals.

Statistical Analysis of Secondary Objective 2

To examine the patterns of failure, we will tabulate the various ways that patients failed up until the time of the analysis. For example, these ways will include local only, local + distant, and distant only.

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