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The role of radiotherapy for patients over age 60 with diffuse large B-cell lymphoma in the rituximab era

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Abstract

The role of consolidative radiotherapy (RT) in patients ≥ 60 years old with DLBCL in the rituximab era is controversial. We examined the impact on disease control and overall survival by the addition of consolidative RT after completion of chemotherapy, while adjusting for known adverse risk factors. Retrospective chart review from 2004 to 2012 of 83 consecutive patients ≥ 60 years old with DLBCL treated in the rituximab era, 68 of which had a complete response to chemotherapy, was performed. Amongst patients with a complete response, consolidative RT use was associated with 100% 5-year local control, improved progression-free survival ($p = 0.047$), and a trend for overall survival ($p = .098$) on multivariate analysis. Amongst all patients, the use of consolidative RT was associated with improved overall survival ($p = 0.03$). The use of consolidative RT should be considered for patients ≥ 60 years old independent of stage and response to chemotherapy.

Keywords

Elderly; diffuse large B-cell lymphoma (DLBCL); radiotherapy

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma, accounting for about one quarter of all non-Hodgkin's lymphomas,[1,2] and typically presents as rapidly enlarging symptomatic lymph nodes which can arise de novo or from transformation of a lower grade B-cell lymphoma.[3] There have been four randomized trials in the pre-rituximab era examining the role of radiotherapy (RT) in limited disease, with mixed results. [4–7] In summary, these trials suggested that combined modality treatment with RT and

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lesser courses of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) was at least as efficacious as full course of chemotherapy.[8] GELA 93-4 looked specifically at older patients and found that RT with CHOP had similar survival rates as CHOP alone [4] and suggested that RT for elderly patients can be omitted all together.

None of these previous trials incorporated rituximab (into an 'R'-CHOP regimen), which has been shown to increase control and survival rates for DLBCL, albeit mostly assessed in advanced disease and elderly patients over age 65.[9–12] In patients less than 60 years old, there is randomized evidence that R-CHOP chemotherapy with RT for bulky and extranodal disease has improved outcomes over CHOP.[13] However the role of RT in elderly patients in the modern rituximab era is not well defined. In light of the paucity of data in examining the effect of RT in elderly patients in the rituximab era, this study was designed to examine the outcomes of a set of elderly patients (age ≥ 60), across all stages, treated in the modern era. Our primary endpoint was looking at both overall survival and control of disease in patients who achieve a complete response to systemic therapy. The secondary objective was to examine involved field failure rates in patients treated with or without RT while including additional prognostic factors such as the International Prognostic Index (IPI) score, size of the disease conglomerate, bone marrow involvement, and involvement of extra nodal sites.

Materials and methods

Patient selection

Under an IRB-approved protocol, the authors reviewed the records of 95 consecutive patients age 60 or older with DLBCL treated with curative intent with conventional, stage appropriate treatment from 2004 to 2012. Twelve patients were excluded because they either refused therapy, had the 'double hit' genetic rearrangement,[14] or did not have a clear histological diagnosis of DLBCL. The treatments were all individualized, but chemotherapy was the primary therapeutic modality with all patients being treated with rituximab-based chemotherapy. Staging was done based on the Lugano classification system.[15,16] Response to systemic therapy was assessed using positron emission tomography-computed tomography (PET-CT) in 82 (99%) of patients using standard criteria prior to 2010,[17] and with implementation of the Deauville criteria for PET response starting in 2010.[18] Consolidative RT was defined as use of RT to treat all initially involved sites of disease after a complete response to systemic therapy. There were four instances where partial responders had treatment that was referred to as consolidative RT, as their disease had completely responded in the majority of sites and only small areas of residual disease remained. These patients received RT to all initially involved sites and residual disease sites as previous series suggest they behave like complete responders.[19]

Two separate analyses were done, one comparing only complete responders to systemic therapy with and without consolidative RT and another comparing all patients, regardless of systemic therapy response, with and without consolidative RT. Prognostic factors that were included were: presence of B-symptoms, bone marrow involvement, LDH level, bulky disease as defined by greater than 5 cm per institutional practice,[20] IPI score, and the number of extranodal sites. Patients were followed with periodic physical exams and imaging. Computed tomographic (CT) scans of regions of disease were obtained as part of

the follow-up process for all patients per standard of care. Local control was defined as time from diagnosis to failure at primary site or time to last follow-up. Distant failure-free survival was defined as time from diagnosis to failure outside primary site or time to last follow-up. Progression-free survival (PFS) was defined as the time from diagnosis to failure (either at primary site or otherwise) or time to last follow-up. Overall survival was defined as time to death or time to last follow-up from diagnosis.

Statistical methods

All statistics were computed using SAS software version 9.3 (Cary, NC). Survival estimates for endpoints were estimated using the Kaplan–Meier product limit method, and survival distributions were compared using the log-rank test.[21] Five-year survival rates for each endpoint are reported. Proportional hazards assumptions were checked for each variable and endpoint. For comparisons, staging was grouped into two categories with stages I and II comprising early stage and stages III and IV comprising late stage. Crude death and failure rates at 5 years and at the end of the study were compared across treatment groups using chi-square tests or Fisher's exact tests, when appropriate. Univariate (UV) Cox proportional hazards models for overall survival, PFS, and local control were fit as a function of demographics, pathological, or clinical tumor features. Univariate analysis tables are reported in an online supplement. Multivariate Cox proportional hazards models for overall survival, PFS, and local control were fit as a function of use of consolidative radiation, stage, B-symptoms, BM involvement, bulky disease, IPI score, and number of extranodal sites. Firth's penalized maximum likelihood estimation was used in the local control models, in order to reduce bias in the parameter estimates and confidence intervals, as well as to handle empty cells.[22,23] Significance was assessed at the 0.05 level. Graphics were created using R version 2.15.1.

Results

Clinical characteristics – all patients

The clinical characteristics of all patients are detailed in Table 1. R-CHOP was the primary systemic therapy in 74 (89.2%) patients, R-CHOP with intrathecal methotrexate (for CNS prophylaxis) was the primary therapy in 7 (8.4%) patients, and VR-CHOP (R-CHOP with bortezomib) was the primary therapy in 2 (2.4%) patients. The average number of cycles of chemotherapy received was 5.51, with a range of 2–8 cycles. The average age at diagnosis of the patients was 69.5 (range of 60–85) years old. The average age at diagnosis of patients who were alive at last follow-up was 68, and of patients who were deceased at last follow-up the age was 71. The average EBRT dose was 34.6 Gy with a range of 30 Gy to 45.9 Gy. Fractionation varied between 1.5 Gy and 3 Gy. Follow-up ranged from 0.88 to 10.25 years, with a median follow-up of 5.23 years. Of the 55 patients (66%) alive at the time of data collection, only 1 was followed for less than 2 years. Of the 32 patients who died, the average length of follow-up was 3.2 years and 3 were Stage I (9%), 10 were Stage II (31%), 5 were Stage III (16%), and 14 were Stage IV (44%).

Chemotherapy response was also assessed. Overall 68 patients (82%) achieved a complete response, 10 patients (12%) achieved a partial response, and 5 patients (6%) achieved no

response. In terms of RT, 34 patients (41%) received RT, either as consolidative therapy (21 patients, 25%), salvage therapy (9 patients, 11%), or palliative therapy (3 patients, 4%). Of these patients, 11 (32%) were treated using intensity modulated radiotherapy (IMRT) with the remaining treated with conventional techniques.

Clinical characteristics – complete responders

Table 2 includes all 68 patients with a complete response to systemic therapy, comparing clinical characteristics of those who received consolidative RT and those who did not. For the complete responders, the median age at diagnosis was 68 years old (range of 60–85). The mean number of chemotherapy cycles given was 5.50, with a range of 2–8 cycles. The chemotherapy delivered was R-CHOP in 63 patients (93%), R-CHOP with intrathecal methotrexate in 4 patients (6%), and VR-CHOP in 1 patient (1%). The mean radiation doses given in the complete responders treated with consolidative RT was 33.6 Gy, with doses ranging from 30 Gy to 41.4 Gy. Follow-up ranged from 1.15 to 10.25 years, with a median follow-up of 6.3 years.

Local control

The 5-year local control rates amongst all patients, regardless of chemotherapy response, receiving consolidative RT was 100% compared with 56.1% ($p < 0.01$) of those who did not. On multivariate analysis of stage, B-symptoms, bone marrow involvement, bulky disease, IPI score, number extranodal sites, and use of consolidative RT, only the use of consolidative RT had a statistically significant improvement in local control ($p = 0.04$) when looking at the entire cohort of 83 patients.

When comparing only patients who had a complete response to systemic therapy, only the use of consolidative RT was associated with improved local control on univariate analysis ($p < 0.01$). On multivariate analysis no variable was associated with improved local control, however there was a trend for consolidative RT having improved local control ($p = 0.08$) as seen in Table 3. At 5 years the local control rate was 100% for those receiving consolidative RT after a complete response versus 65% in those who had complete response but did not receive consolidative RT ($p < 0.01$) as seen in Figure 1.

Distant disease control

On univariate analysis of distant failure-free survival amongst the entire cohort of 83 patients, lack of bone marrow involvement ($p < 0.01$) and not having extranodal disease ($p = 0.01$) were associated with improvement. On multivariate analysis of stage, B-symptoms, bone marrow involvement, bulky disease, IPI score, number extranodal sites, and use of consolidative RT, only lack of bone marrow involvement was significantly associated with improved distant failure-free survival ($p = 0.046$) amongst all patients.

Amongst the 68 patients having a complete response to chemotherapy, the 5-year distant disease control was 81% in those that received consolidative RT versus 70% in those who did not ($p = 0.11$). The average time to distant failure in patients achieving a complete response was 18.2 months in those who received consolidative RT and 14.1 months in those who did not.

Progression-free survival

On univariate analysis of PFS of the entire cohort of patients, the use of consolidative RT ($p = 0.01$), lack of bone marrow involvement ($p = 0.01$), and not having extranodal disease ($p = 0.04$) were associated with improved PFS. On multivariate analysis of the entire population, only the use of consolidative RT was associated with improved PFS ($p = 0.01$). At 5 years the PFS was 79% in those receiving consolidative RT versus 49% in those that did not ($p = 0.01$), among all 83 patients.

Amongst only the patients having a complete response to chemotherapy, use of consolidative RT ($p = 0.05$) and bone marrow involvement ($p = 0.05$) were associated with improved PFS on univariate analysis. Only the use of consolidative RT was associated with improved PFS on multivariate analysis ($p = 0.04$) as seen in Table 4. At 5 years the PFS among complete responders was 79% in those receiving consolidative RT versus 57% in those who did not ($p = 0.06$) as seen in Figure 2.

Overall survival

Among the entire patient subset, the use of consolidative RT ($p = 0.03$), Stage I or II disease ($p = 0.03$), and lack of bone marrow involvement ($p < 0.01$) were the factors associated with improved overall survival on multivariate analysis. The 5-year overall survival rate was 89% in patients receiving consolidative RT versus 67% in those who did not ($p = 0.17$), regardless of response to chemotherapy.

In the patients who achieved a complete response to chemotherapy, bulky disease ($p = 0.04$) and bone marrow involvement ($p = 0.02$) were associated with lower overall survival on multivariate analysis (Table 5). There was a trend toward consolidative RT improving survival ($p = 0.09$). The 5-year overall survival rates in complete responder patients was 87% in those that received consolidative RT and 75% in those who did not ($p = 0.21$), as seen in Figure 3.

Complications/toxicity

No patient suffered a severe complication or severe acute toxicity during the treatment process. One patient had to have his systemic therapy of R-CHOP stopped after 5 of 6 planned cycles due to mucositis. One patient who received systemic therapy alone passed away 3 months after the completion of therapy due to a myocardial infarction. All patients who were prescribed RT completed the full course. There were no long-term severe toxicities recorded.

Discussion

There is minimal literature reviewing the use of consolidative RT in the modern R-CHOP era for elderly patients. Past concerns have included subjecting this particular group of patients to possibly increased rates of toxicity with RT, without benefits in terms of overall survival.[24] Our study demonstrated that radiotherapeutic intervention could be safely delivered to this subgroup of older patients as there were no treatment-related toxicities or issues. Amongst patients who achieve a complete response to chemotherapy, our study

indicates that using consolidative RT improves local control and PFS with a trend toward improving overall survival. When comparing complete responders to partial responders we tended to see a trend toward worse PFS and overall survival in the non-responders when radiation was withheld. When we analyzed all patients (regardless of chemotherapy response) and compared those that received consolidative RT versus those who did not, we saw a local control and overall survival benefit. These findings at least suggest a possibility that RT can ‘make up’ for less than a complete response. Our findings are in agreement with the recently published RICOVER-60 trial which compared outcomes against a cohort receiving the same systemic therapy but without RT (RICOVER-noRT),[25] and our institutional study looking at stage III/IV patients regardless of age.[26] The RICOVER-60 trial showed local control and PFS benefit, but not an overall survival benefit. However when analyzed per actual treatments delivered, there was an overall survival benefit in patients with bulky disease. This was due to the fact that there were patients that died after chemotherapy and never made it to RT.[25]

Additionally, it is important to consider that the subset of patients receiving consolidative RT where not specifically selected with good prognostic factors. In our patient group receiving consolidative RT amongst complete responders, 52% were stages III/IV and 29% had two or more extranodal sites of disease. Five-year overall survival rates were higher in those that received consolidative RT (89.2% versus 67.0%) amongst all patients regardless of chemotherapy response. Additionally there were only 4 patients who had disease progression after receiving consolidative RT. All 4 of these patients had disease progression outside of the site that received the radiation; none had progression within the radiated site.

In current practice, the use of RT in the management of elderly patients with advanced stage DLBCL is still controversial. One large retrospective review in the modern R-CHOP era also showed improvement of overall survival in patients receiving consolidative RT.[27] However this analysis did not focus on the elderly population and included patients over a wide age range. This study did show that adding RT improved survival outcomes across all stages, and showed that response to chemotherapy and use of RT were the strongest prognostic factors affecting disease progression and survival. Another retrospective review examined the use of consolidative RT in Stage III/IV patients with DLBCL with R-CHOP and found that consolidative RT improved PFS without an improvement of overall survival.[28] This study focused only on patients who achieved a complete response to chemotherapy and was not limited to patients older than 60 years of age. A recent review of the National Cancer Data Base, where 68% of the patients were 60 years or older, also suggested that consolidative RT may have an overall survival benefit when compared with chemotherapy alone.[29]

Our study also examined other known prognostic factors and their relationship to outcomes. Bone marrow involvement, bulky disease, and advanced stage disease were statistically significantly associated with worse overall survival, which is consistent with the literature. [4–10] Our overall outcomes in terms of PFS and overall survival are in line with the published literature.[4,11,28,30]

Our series has some recognized limitations of retrospective reviews, namely dependence on the medical record for patient’s that have passed away or been lost to follow-up.

Additionally there is selection bias as with any chart review as there is no randomization of patients. Our sample size is adequate in the literature, as we limited this study to only patient's older than 60 treated recently and with modern systemic therapy. We likely lost some statistical accuracy by splitting patients that received RT into those that had complete response and those that had complete response as well as partial response.

In summary, our series shows that RT can be implemented safely in patients 60 years of age or older with DLBCL, regardless of stage or chemotherapy response, with benefits in terms of local control and overall survival, even in the modern rituximab era. While the overall survival significance was lost when comparing only complete responders, our series suggests that RT may be used to 'make-up' what is lost in patients having only a partial response to systemic therapy. It is now our institutional practice to recommend consolidative RT in any patient who achieves a complete response to chemotherapy, regardless of age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Local control compared between patients who all had a complete response to chemotherapy, with or without consolidative radiotherapy.

Figure 2.

Progression-free survival compared between patients who all had a complete response to chemotherapy, with or without consolidative radiotherapy.

Figure 3.
Overall survival compared between patients who all had a complete response to chemotherapy, with or without consolidative radiotherapy.

Table 1

Descriptive population statistics of the 83 patients age 60 or older with DLBCL.

Variable	Level	<i>n</i> = 83	%
Gender	Male	39	47.0
	Female	44	53.0
Stage	1	11	13.3
	2	21	25.3
	3	22	26.5
	4	29	34.9
B-symptoms	No	61	73.5
	Yes	22	26.5
BM involvement	No	69	83.1
	Yes	14	16.9
LDH level	Normal	47	57.3
	Elevated	35	42.7
	Missing	1	-
Bulky disease	5cm	44	53.0
	>5cm	39	47.0
IPI score	1	26	31.3
	2	16	19.3
	3	26	31.3
	4/5	15	18.1
Number of extranodal sites	0	25	30.1
	1	29	34.9
	2+	29	34.9
Presenting site (diaphragm)	Above	25	30.1
	Below	18	21.7
	Both	40	48.2
Consolidative radiotherapy	No	62	74.7
	Yes	21	25.3
Any radiotherapy use	No	49	59.0
	Yes	34	41.0

Table 2

Descriptive clinical characteristics of complete responders to systemic therapy.

Variable	Level	No Consolidative RT (n = 51)	Consolidative RT (n = 17)
Stage	1	5 (10%)	4 (24%)
	2	11 (22%)	4 (24%)
	3	15 (29%)	5 (28%)
	4	20 (39%)	4 (24%)
B-symptoms	No	42 (82%)	11 (65%)
	Yes	9 (8%)	6 (35%)
BM involvement	No	45 (88%)	14 (82%)
	Yes	6 (12%)	3 (8%)
LDH level	Normal	32 (63%)	6 (35%)
	Elevated	18 (35%)	11 (65%)
	Missing	1 (2%)	–
Bulky disease	5.0 cm	28 (55%)	9 (53%)
	>5.0 cm	23 (45%)	8 (47%)
IPI score	1	15 (29%)	5 (29%)
	2	12 (24%)	2 (12%)
	3	15 (29%)	6 (35%)
	4/5	9 (18%)	4 (24%)
Number of extranodal sites	0	16 (31%)	5 (29%)
	1	17 (33%)	7 (42%)
	2+	18 (36%)	5 (29%)
Presenting site (diaphragm)	Above	11 (22%)	8 (47%)
	Below	12 (24%)	3 (18%)
	Both	28 (54%)	6 (35%)

Table 3

Multivariate analysis of different clinical factors and their association with local control amongst only patients with a complete response to chemotherapy.

Covariate	Level	Hazard ratio	<i>p</i> Value
Consolidative radiation	Yes	0.08 (0.00–1.40)	0.084
	No	–	
Stage	I/II	0.86 (0.09–7.89)	0.895
	III/IV	–	
B-symptoms	Yes	0.36 (0.08–1.57)	0.173
	No	–	
BM involvement	Yes	1.33 (0.34–5.17)	0.684
	No	–	
Bulky disease	≤5cm	0.72 (0.25–2.09)	0.542
	>5cm	–	
IPI score	2	1.09 (0.14–8.62)	0.671
	3	2.44 (0.16–38.18)	
	4/5	1.21 (0.05–27.41)	
	1	–	
Number of extranodal sites	1	1.20 (0.28–5.07)	0.758
	2+	1.85 (0.36–9.41)	
	0	–	

Table 4

Multivariate analysis of different clinical factors and their association with progression-free survival in patients with a complete response to chemotherapy.

Covariate	Level	Hazard ratio	<i>p</i> Value
Consolidative radiation	Yes	0.28 (0.08–0.99)	0.047
	No	–	
Stage	I/II	0.45 (0.06–3.64)	0.454
	III/IV	–	
B-symptoms	Yes	1.19 (0.47–3.04)	0.717
	No	–	
BM involvement	Yes	2.63 (0.85–8.19)	0.094
	No	–	
Bulky disease	≤5cm	0.72 (0.31–1.68)	0.447
	>5cm	–	
IPI score	4/5	0.80 (0.05–12.34)	0.206
	3	2.03 (0.17–24.21)	
	2	0.47 (0.08–2.91)	
	1	–	
Number of extranodal sites	2+	2.51 (0.58–10.77)	0.389
	1	1.93 (0.60–6.18)	
	0	–	

Table 5

Multivariate analysis of different clinical factors and their association with overall survival in patients with a complete response to chemotherapy.

Covariate	Level	Hazard ratio	<i>p</i> Value
Consolidative radiation	Yes	0.32 (0.08–1.23)	0.098
	No	–	
Stage	I/II	0.10 (0.01–1.38)	0.085
	III/IV	–	
B-symptoms	Yes	1.84 (0.61–5.56)	0.280
	No	–	
BM involvement	Yes	5.48 (1.30–23.13)	0.021
	No	–	
Bulky disease	≤5cm	0.33 (0.11–0.97)	0.043
	>5cm	–	
IPI score	4/5	4.33 (0.14–136.52)	0.424
	3	8.50 (0.40–179.66)	
	2	2.16 (0.29–16.14)	
	1	–	
Number of extranodal sites	2+	0.92 (0.16–5.20)	0.929
	1	1.21 (0.35–4.24)	
	0	–	