Studies on non-hodgkin’s lymphoma

In the year 2018, Non-Hodgkin’s lymphoma (NHL) is the more predominant subtype lymphoma in the United States. Patient risk factors that have been linked with an enhanced incidence for the development of NHL include: advanced age, male gender, Caucasian race, genetic diseases, infectious agents, and environmental elements. Histologically, NHL can be acquired from malignant B or T cells and their precursors, however in the United States it is more common to see NHL derive from a B cell origin. Patients with NHL may experience B-symptoms similar to Hodgkin’s lymphoma but may also present with a broader array of symptoms depending on location of involvement. As with Hodgkin’s lymphoma, our goal of treatment for NHL patients are to minimize symptoms, mitigate risk of toxicities, induce remission and ultimately cure patients (p 2218-2223). [1]

Clinical Research on Non-Hodgkin’s Lymphoma

Recher C et al.

Purpose: This study centers on establishing a first-line chemotherapeutic regimen for patients ranging from 18 to 59 years of age, afflicted with treatment-naïve diffuse large B-cell lymphoma (DLBCL).

Study Design: Open label, multicenter, phase III, randomized control trial

Methods: Patients with DLBCL were selected from seventy-three hematology centers located in France, Belgium and Switzerland. The study occurred over a 5 year time frame from December 2003 to December 2008. Two discrete treatment regimens were compared, R-CHOP and R-ACVBP. The primary endpoint studied is event-free survival from DLBCL. The secondary endpoints

are treatment response, disease-free survival, progression-free survival, overall survival, CNS progression, and safety. This study used an intent-to-treat analysis with a follow-up at 44 months. Table 1 lists the chemotherapy regimens of R-CHOP and R-ACVBP. [2]

TABLE 1: CHEMOTHERAPY REGIMENS OF R-CHOP AND R-ACVBP [2]

R-CHOP ARM *(8 CYCLES REPEATED EVERY 3 WEEKS*)		R-ACVBP ARM *(4 CYCLES REPEATED EVERY 2 WEEKS)*	
1 Induction Cycle consists of the following		1 Induction Cycle consists of the following	
375 mg/m^2	Rituximab	375 mg/m^2	Rituximab
75 mg/m^2	Doxorubicin	75 mg/m^2	Doxorubicin
1200 mg/m	Cyclophospham	1200	Cyclophospham

		mg/m 2	ide on day 1
2		2 mg dose	Vindesine
750 mg/m 2	Cyclophosphamide	10 mg/m 2	Bleomycin on day 1 and day 5
1.4 mg/m 2	Vincristine on day 1 (max of 2 mg/dose)	60 mg/m 2	Prednisone on day 1 and day 5
		*Filgrastim can be given SQ on days 6-13	
60 mg/m 2	Prednisone on day 1 and day 5	* Consolidation cycle consists of methotrexate, leucovorin rescue, rituximab, etoposide, ifosfamide, and cytarabine	

Inclusion Criteria

International Prognostic Index of 1 (raised lactate dehydrogenase, Ann Arbor stage 3-4, ECOG 2-4)

At least three months of minimum life expectancy

Negative results for infections that include HIV, hepatitis B or hepatitis C

Exclusion Criteria

T-cell lymphoma or indolent lymphoma subtypes

CNS involvement

Contraindications to any chemotherapeutic agents

Poor renal function (creatinine > 150 mmol/L)

Poor hepatic function (total bilirubin > 30 mmol/L or transaminase 2 – 5 X’s ULN)

Poor bone marrow function (neutrophil < 1. 5 X 10^{9} /L or PLT < 100 X 10^{9} /L)

Any history of cancer within the past 5 years

Treatment with any investigational drugs within 30 days before this study

Statistics: In order to achieve 100 events with an 80% power, this study needed at least three hundred and eighty patients. An interim analysis was conducted after 40 events (2 years; A = 0. 0008) and a final analysis after 100 events (3 years; A = 0. 05).

Results: The results of this study can be summarized in Table 2 listed below.

TABLE 2: RESULTS OF R-CHOP AND R-ACVBP CHEMOTHERAPY REGIMENS [2]

CATEGORY	R-CHOP ARM	R-ACVBP ARM	P VALUE
3-YR event-free survival	67%	81%	P = 0.0035
3-YR progression-free survival	73%	87%	P = 0.0015
3-YR overall survival	84%	92%	P = 0.0071
Serious adverse effects	15%	42%	N/A
Febrile neutropenia	9%	38%	N/A

Conclusion: There were great improvements in primary and secondary endpoints in patients receiving R-ACVBP compared to R-CHOP. For patients that may relapse, RCHOP was be a subtherapeutic option. The downside to R-ACVBP is its malevolent side effect profile versus R-CHOP. For younger

patients with low-to-intermediate risk of diffuse large B-cell lymphoma, R-ACVBP may be a good first-line approach to improve survival. [3]

Cunningham D et al.

Purpose: In patients of all ages, this study will determine if the intense regimen R-CHOP 14, has better overall survival compared to the standard regimen R-CHOP 21.

Study Design: Open label, Phase III, randomized control trial

Methods: 1080 untreated LBCL patients were selected from one hundred and nineteen United Kingdom centers. Patients were randomly assigned to receive R-CHOP 14 regimen or R-CHOP 21 regimen. This study took place from March 2005 to November 2008. Five hundred and forty patients were in each arm and the median follow-up was 46 months. Patients were assessed every 3 months for 1 year, then every 6 months for 2 years, and then every year thereafter. The primary endpoint that was studied was overall survival in patients. Secondary endpoints include: progression-free survival, response, and adverse effects. Table 3 lists a summary of the chemotherapy regimens of R-CHOP 14 and R-CHOP 21.

TABLE 3: CHEMOTHERAPY REGIMENS OF R-CHOP 14 AND R-CHOP 21 [3]

R-CHOP 14 ARM	R-CHOP 21 ARM
TOTAL OF 6 CYCLES GIVEN EVERY 14	*TOTAL OF 8 CYCLES GIVEN EVERY 21*

	DAYS	
	750 mg/ m^2	Cyclophospham ide
	50 mg/ m^2	Doxorubicin
DAYS AND THEN AN ADDITIONAL 2 CYCLES OF RITUXIMAB EVERY 14 DAYS	2 mg dos e	Vincristine
	375 mg/ m^2	Rituximab on day 1
	100 mg	Prednisolone on day 1-5

75 0 mg /m 2	Cyclophospham ide	

50 mg /m 2	Doxorubicin	
1.4 mg /m 2	Vincristine (Max dose 2 mg/dose)	
375 mg /m 2	Rituximab on day 1	
40 mg /m 2	Prednisolone on day 1-5	

Inclusion Criteria

At least 18 years old with untreated diffuse large B-cell lymphoma

Ann Arbor bulky stage 1A, 1B-IV

Good performance status (WHO grade 0-2)

Good cardiac, renal, and hepatic function

Good hematological function (neutrophil > 1. 5 X 10^{9} /L or PLT > 100 X 10^{9} /L)

Exclusion Criteria

T-cell lymphoma, transformational follicular lymphoma, or indolent lymphoma subtypes

CNS involvement

Positive results for infections: HIV, hepatitis B, or hepatitis C

Active malignancy in the past 10 years

Statistics: In order to detect a 5% significance and a 90% power, the intention-to-treat analysis must include 330 overall survival events within 2 years.

Results: The primary endpoint (overall survival) in R-CHOP 14 was not met compared to R-CHOP 21. R-CHOP 14 did not improve response, progression free survival, or safety. However, this study was not adequately powered.

Table 4 lists the results of R-CHOP 14 and R-CHOP 21

TABLE 4: RESULTS OF R-CHOP 14 AND R-CHOP 21 CHEMOTHERAPY REGIMENS [3]

CATEGORY	R-CHOP 14	R-CHOP 21	P VALUE
2 YR Overall Survival	82. 7%	80. 8%	P = 0. 3763
2 YR Progression Free survival	75. 4%	74. 8%	P = 0. 5907
Grade 3 or 4 neutropenia	31%	60%	P = < 0. 0001
Grade 3 or 4 thrombocytopenia	9%	5%	P = 0. 01
Febrile neutropenia	11%	5%	P = 0. 0007
Infection	23%	18%	N/A

Conclusion: RCHOP 14 is not deemed to be superior to R-CHOP 21. Therefore, R-CHOP 21 remains first-line treatment option for recently diagnosed DLBCL patients.[3]

Odejide O et al.

Purpose: In a cohort of at least 66 years old patients, this study focused on the two most common treatment strategies (abbreviated R-CHOP of 3-4 cycles + radiation or full course R-CHOP of 6-8 cycle).

Study Design: This is a comparative effectiveness study that used registry and claims data in the United States.

Methods: The original cohort included 4, 322 patients that were selected from the National Cancer Institute SEER registry (1999-2009) linked to Medicare claims data (1999-2010). The study also used Lymphoma CRIS as another source of data. The final cohort consisted of 874 patients with 359 patients (41%) receiving 3-4 cycles of R-CHOP + radiation therapy (XRT) and 515 patients (59%) receiving 6-8 cycles of R-CHOP. The median age was 74 years old and the median follow-up was 4. 2 years. The primary endpoint that was studied was overall survival in patients and the secondary endpoints include: time to second-line treatment and adverse effects listed in table five.

Inclusion Criteria

Diagnosed stage 1 or stage 2 diffuse large B-cell lymphoma and at least 66 years old

Continuous enrolled in Medicare Part A and Part B with no HMO coverage

Survived at least 6 months following diagnosis of lymphoma

No diagnosed ESRD or disability

Exclusion Criteria

Patients who received radiation therapy before chemotherapy

Bulky stage 2 disease lymphoma

Statistics: A 2 sided P <0. 05 was used to determine statistical significance. The study used propensity score matching and odds ratio in the calculations. Odds ratio less than 1 indicated that there is a better outcome for patients receiving 3-4 cycles of abbreviated R-CHOP + radiation therapy instead of 6-8 cycles of standard R-CHOP alone.

Results: The 5-yr overall survival in the abbreviated R-CHOP + radiation therapy was 77% and in full course RCHOP group it was 76%. The P value = 0. 87. Table 5 contrasts adverse events in the abbreviated R-CHOP to standard course R-CHOP using adjusted propensity score and odds ratio. The odds ratio is used in the study to provide association between two groups. It represents the odds that an outcome will occur given a particular exposure compared to the odds of the outcome occurring with another exposure. In this study, odds ratio is defined: if less than 1, then there are better outcomes for patients receiving 3-4 cycles of R-CHOP plus RT instead of standard R-CHOP.

TABLE 5: ADVERSE OUTCOMES ASSOCIATED WITH TREATMENT USING ADJUSTED PROPENSITY SCORES OF ABBREVIATED R-CHOP WITH XRT TO STANDARD R-CHOP [4]

Outcomes	Odds Ratio	P-Value

	(Abbreviated to Standard)	
Hospitalization	0. 83	0. 17
Fever	0. 6	0. 002
Neutropenia	0. 63	0. 002
Fever + Neutropenia	0. 27	< 0. 001
Infections	0. 98	0. 89
CHF	0. 98	0. 95
Poor functional status	1. 14	0. 5

Conclusion: Abbreviated R-CHOP with radiation therapy may be better tolerated in elderly patients with limited stage DLCBL, however both treatment options ostensibly provide equivalent overall patient survival rates. [4]

Summary

These studies represent some of the important clinical trials in the treatment of Non-Hodgkin’s Lymphoma. With continued research, we can further define the optimal regimens and reduce toxicities associated with chemotherapy.

References

1. Chan, Alexandre. “ Chapter 132: Lymphomas.” *Pharmacotherapy: A Pathophysiologic Approach* , edited by Jolynn Sessions, 10th ed., McGraw-Hill Education, 2017, pp. 2218–2223.
2. Recher C, Coiffier B, Haioun C, et al. Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial. Lancet 2011; 378: 1858-1867. http://www. ncbi. nlm. nih. gov/pubmed/22118442.
3. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet 2013; 381: 1817-1826. http://www. ncbi. nlm. nih. gov/pubmed/23615461.
4. Odejide OO, Cronin AM, Davidoff AJ, et al. Limited stage diffuse large B-cell lymphoma: comparative effectiveness of treatment strategies in a large cohort of elderly patients. Leuk Lymphoma 2015; 56: 716-724. http://www. ncbi. nlm. nih. gov/pubmed/24913508.