Radiotherapy for advanced-stage aggressive non-Hodgkin lymphoma

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Radiotherapy for advanced-stage aggressive non-Hodgkin lymphoma (Protocol)

Yap E, Law ZK, Wan Jamaludin WF, Abdullah NMA, Abdul Wahid SF

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Radiotherapy for advanced-stage aggressive non-Hodgkin lymphoma

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the benefits (overall survival, progression-free survival, event-free survival and quality of life) and harms (toxicities) of radiotherapy for people with advanced aggressive non-Hodgkin lymphoma (NHL).

BACKGROUND

Description of the condition

Aggressive B-cell non-Hodgkin lymphomas (NHLs) are the most common lymphoid neoplasms in adults, accounting for about 4% to 10% of all cancers worldwide (Müller 2005; Weisenburger 1994), of which diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype (Harris 1994; Harris 1999). As of 2014, the American Cancer Society estimated that there would be 70,800 new cases and 18,990 deaths of people with NHL in the United States. The five year survival rate for NHL is about 71% for all patients (Siegel 2014).

Staging of the disease is performed according to the Ann Arbor staging model (Carbone 1971; Lister 1989), an anatomical-based model in which:

- stage I indicates that the cancer involves one lymph node region;
- stage II indicates that the cancer involves two lymph node regions on the same side of the diaphragm;
- stage III indicates that the cancer involves lymph nodes on both sides of the diaphragm; and
- stage IV indicates diffuse extralymphatic involvement.

Stage I and II are considered early stage whereas bulky stage II, stage III and IV are advanced stage. Early-stage and advanced-stage aggressive NHLs are treated differently. People with early-stage disease are usually treated with a combination of short courses of chemotherapy followed by radiation of affected sites, and generally have good prognosis (Horning 2004; Miller 1998). About 60% to 70% of people with aggressive NHL present in advanced stages of the disease (Ries 2008). Aside from being an independent adverse prognostic factor, advanced stage also presents a
different treatment paradigm to the treating clinician. People with advanced-stage NHL require full dose rituximab-based chemotherapy to attain the best chance of a complete response. Interestingly, further addition of these agents has not been shown to have mortality benefits, with overall survival estimated as between 50% and 54% (Habermann 2006; Miller 1998). Although the era of rituximab has significantly improved the treatment and prognosis of CD20+ B cell lymphomas, people with aggressive NHL still have high risk of disease relapse and death (Coiffier 2010; Schulz 2007).

**Description of the intervention**

Radiotherapy (RT) refers to the use of ionising radiation to kill malignant cells. It is an effective modality in treating lymphomas, with a proven track record in early-stage aggressive NHL, as well as in bulky disease, which by itself is an independent adverse prognostic factor (Pfreundschuh 2006). However, due to a high relapse rate using RT alone, systemic immuno-chemotherapy has become the primary modality of treatment. The use of RT nowadays is limited to the period after systemic therapy, either as consolidative therapy to initial sites or to eliminate residual disease. RT’s effectiveness in eradicating residual disease and improving local control has been shown, but the question of whether improved local control translates to a survival benefit remains unanswered. Nevertheless, the routine addition of RT to areas of previously bulky diseases or residual masses in advanced NHLs is not practiced universally (Held 2014), and is not explicit in the National Comprehensive Cancer Network guidelines. Thus, there is a lack of consensus and guidelines on the role of RT, the doses required and the optimum RT field in NHL compared to the data available for Hodgkin’s lymphoma (Specht L 2013). Most are in agreement that in the multimodality setting, a lower radiation dose for control can be used, but there are disagreements on the minimum dose needed (Ferreri 2000; Kelsey 2010), especially when dealing with residual diseases which are bulky.

**Why it is important to do this review**

The current standard immuno-chemotherapy has limited efficacy in advanced-stage NHL. To the best of our knowledge, there is no systematic review with meta-analysis on this subject, although the authors of a narrative review recommended RT to bulky sites (Wirth 2007). Moreover the role of radiotherapy in advanced-stage NHL has yet to be described definitively.

**OBJECTIVES**

To assess the benefits (overall survival, progression-free survival, event-free survival and quality of life) and harms (toxicities) of radiotherapy for people with advanced aggressive non-Hodgkin lymphoma (NHL).

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We will include randomised controlled trials which evaluated systemic chemotherapy with radiotherapy (RT) compared with systemic chemotherapy alone in people with advanced aggressive NHL.

**Types of participants**

Adult or paediatric patients newly diagnosed with advanced-stage aggressive NHL who received systemic chemotherapy with or without rituximab with subsequent complete response (CR) or partial response (PR). Trials that include patients who did not achieve the above response rates will be excluded. We will also exclude people with primary central nervous system lymphoma, primary gastrointestinal lymphoma, primary breast lymphoma, or primary testicular lymphoma.
Types of interventions

Experimental intervention
Radiotherapy (RT) used in the consolidation phase on people with advanced, aggressive NHL who have achieved complete response or partial response from chemotherapy with rituximab (immunochemotherapy) or without rituximab. There is no restriction on dose, frequency intensity or duration of RT.

Comparator intervention
Observation only in people with NHL who have achieved complete response or partial response from chemotherapy with or without rituximab. The (immuno)-chemotherapy regimen should be the same in both arms, with equal cycles in both arms. We will exclude trials that include treatment in the disease-relapse setting.

Types of outcome measures

Primary outcomes
Overall survival (OS) defined as the time from entry onto the clinical trial (random assignment in a phase III study) until death as a result of any cause (Cheron 2007).

Secondary outcomes
- Progression-free survival (PFS), defined as the interval from time of randomisation/study entry to:
  - the first recurrence of disease (progression or relapse) that is histologically confirmed or requires treatment; or
  - death from any cause.
- Event-free survival (EFS), defined as the interval from time of randomisation/study entry to an event (relapse, progression or death).
- Time to progression (TTP), defined as the time from study entry until documented lymphoma progression or death as a result of lymphoma.
- Local control, defined as the absence of disease recurrence within the previously administered RT field in patients who received consolidation RT or at initially involved sites in both patients who did and did not receive RT, timed from the date of completion of chemotherapy, regardless of disease status outside of the field.
- Adverse events.
- Quality of life.

Search methods for identification of studies

Electronic searches
We will search:
- MEDLINE (Ovid) (January 1946 to present) (Appendix 1)
- EMBASE (1974 to present) (Appendix 2)
- the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, latest issue) (Appendix 3)
- http://www.clinicaltrials.gov/

We will not apply any language restriction. We will use the search algorithms outlined by the Trials Search Coordinator of the Cochrane Haematological Malignancies Group (CHMG). The search strategies for MEDLINE, EMBASE and CENTRAL are outlined in Appendix 1, Appendix 2 and Appendix 3.

Searching other resources
We will search reference lists of all primary studies and review articles for additional references. Using the terms “Non-Hodgkin’s lymphoma” and “radiotherapy” we will handsearch the conference proceedings of the following (that are not available in CENTRAL):
- American Society of Hematology (1990 to present)
- American Society of Clinical Oncology (1990 to present)
- European Society for Medical Oncology (1990 to present)
- European Haematology Association (1990 to present)

We will contact the relevant experts in the field of radiotherapy in NHL for further information.

Data collection and analysis

Selection of studies
Two review authors will independently screen the abstracts of all studies identified for their eligibility for inclusion. If that is insufficient for a decision to be made, the full-text article will be retrieved for a full review. Any disagreements will be resolved by consensus, or by referring to a third review author. The number of studies identified, excluded and included will be documented according to PRISMA (Moher 2010).

Data extraction and management
We will contact authors of individual studies for additional information if required. We will use a standardised data extraction form containing the following items (Higgins 2011a):

Source
- Study ID (created by review author).
- Report ID (created by review author).
- Review author ID (created by review author).
Eligibility
- Confirm eligibility for review.
- Reason for exclusion.

Methods
- Study design.
- Total study duration.
- Sequence generation.
- Allocation sequence concealment.
- Blinding.
- Other concerns about bias.

Participants
- Total number.
- Setting.
- Diagnostic criteria.
- Age.
- Sex.
- Country.
- Co-morbidity.

Interventions
- Total number of intervention groups.

For each intervention and comparison group of interest:
- Specific intervention.
- Intervention details (if feasible).

Outcomes
- Outcomes and time points (i) collected; (ii) reported.

For each outcome of interest:
- Outcome definition (with diagnostic criteria if relevant).
- Unit of measurement (if relevant).
- For scales: upper and lower limits, and whether high or low score is good.

Results
- Number of participants allocated to each intervention group.

For each outcome of interest:
- Sample size.
- Missing participants.
- Summary data for each intervention group.
- Estimate of effect with confidence interval; P value.
- Subgroup analyses.

Miscellaneous
- Funding source.
- Key conclusions of the study authors.
- Miscellaneous comments from the study authors.
- References to other relevant studies.

Assessment of risk of bias in included studies
We will assess the risk of bias based on the approach described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011b) which outlined the following domains:
- random sequence generation
- allocation concealment
- blinding of participants and personnel
- blinding of outcome assessment
- incomplete outcome data
- selective outcome reporting
- other potential sources of bias

We will accord a judgment of low or high risk of bias if there is sufficient information in the study report, and justify our grade with a quote from the study in the 'Risk of bias' table. If there is insufficient information available from the study to enable a judgment, we will grade the risk of bias as 'unclear'. We will document these assessments in a 'Risk of Bias' table.

Measures of treatment effect
For dichotomous outcomes, we will use risk ratio (RR) and 95% confidence interval (CI). For time-to-event data, we will use hazard ratio (HR) and 95% CI. If HR is not reported, it will be calculated from the observed minus expected number of events (O-E) and variance for each end point. If these are not reported as well, HR will be calculated with data extracted from Kaplan-Meier curves with the methods described by Tierney et al. (Tierney 2007).

For continuous outcomes, we will use mean difference, or standardised mean difference if conceptually similar outcomes are measured in different scales. In this case, we will adjust all the scales to achieve a consistent direction of effect.

Unit of analysis issues
Groups of individuals randomised together to the same intervention (i.e. cluster-randomised trials)
We do not expect any cluster-randomised trials due to the inherent nature of the disease and intervention.

Cross-over trials
We do not expect any studies with cross-over design due to the intervention being given on a consolidative basis.

Multiple observations for the same outcome
For multiple observations, we will select the longest follow-up from each study (Higgins 2011c).

Dealing with missing data
If needed, we will contact the authors of primary studies to request missing data. We will also make explicit assumptions of any methods used. We will impute missing data for participants who were lost to follow up after randomisation (dichotomous data) assuming worse-case scenario for missing individuals (Higgins 2011d).
We will then perform sensitivity analyses to assess how sensitive results are to reasonable changes in the assumptions that are made. We will address the potential impact of missing data on the findings of the review in the Discussion section. Assuming a worst-case scenario, the time point when the individual patients were lost to follow-up is assumed to be the time point for the worst outcome, i.e. death.

Assessment of heterogeneity

We will calculate statistical heterogeneity using the Chi² test and I² statistic. We will use a P value of less than 0.10 to indicate significant heterogeneity. We will interpret I² based on the following parameters (Higgins 2011c):

- 0% to 40% - heterogeneity possibly not important
- 30% to 60% - moderate heterogeneity
- 50% to 90% - substantial heterogeneity
- 75% to 100% - considerable heterogeneity

Assessment of reporting biases

If at least ten trials are included in the meta-analysis, we will construct a funnel plot and statistically test potential publication bias by using a linear regression test. We will consider a P value of less than 0.1 to indicate significant heterogeneity (Sterne 2011).

Data synthesis

We will perform meta-analysis using the Review Manager 5.3 software (RevMan 2014) (Higgins 2011c). We will pool log HR for time-to-event outcomes using the inverse variance method (HR < 1.0 is in favour of consolidative RT). We will first use a fixed-effect model, and repeat the primary analysis using a random-effects model (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

We plan to perform the following subgroup analyses:

- Different risk groups based on the International Prognostic Index (IPI)
- Difference between bulky and non-bulky disease
- Difference between participants who received rituximab and those who did not
- Different age groups
- Different doses of radiotherapy (RT)
- Different modalities of RT i.e. involved-field versus extended-field RT

Sensitivity analysis

We will perform a sensitivity analysis comparing the random-effects and the fixed-effect model if the I² statistic is > 0%.

ACKNOWLEDGEMENTS

We thank the Cochrane Haematological Malignancy Group for their support. We are also grateful to Associate Professor Lai Nai Ming for his advice in writing the protocol of this systematic review.

REFERENCES

Additional references

Carbone 1971

Cheson 2007

Coiffier 2010
Radiotherapy for advanced-stage aggressive non-Hodgkin lymphoma (Protocol)

Held 2014

Harris 1999

Habermann 2006

Higgins 2011d

Hornung 2004

Kelsey 2010

Lister 1989

Miller 1998

Moher 2010

Pfreundschuh 2006

RevMan 2014

Ries 2008
Ries LAG, Melbert D, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, et al. SEER Cancer Statistics...
Rübe 2001

Schlembach 2000

Shi 2013

Siegel 2014

Specht I. 2013

Sterne 2011

Tierney 2007

Weisenburger 1994

Wirth 2007

* Indicates the major publication for the study
Appendix 2. EMBASE search strategy

1. exp nonhodgkin lymphoma/
2. (non-hodgkin* or non hodgkin* or nonhodgkin* or no hodgkin* or nhl).af.
3. (lymph* adj2 sarcom*).af.
4. lymphosarcom*.af.
5. (reticulum adj2 sarcom*).af.
6. (lymphom* adj2 (cleaved* or noncleaved* or grad* or mixed-cell* or pleomorphic*)).af.
7. (lymphom* adj2 (cleaved* or noncleaved* or grad* or mixed-cell* or pleomorphic* or diffus*)).af
8. (bcell* or b-cell*).af.
9. or/ 1-8
10. *LYMPHOMA/
11. (lymphom* or linfom*).af.
12. exp HEMATOLOGIC NEOPLASMS/
13. (lympho* adj2 (neoplasm* or malign* or tumor* or tumour* or sarcom*)).af.
14. (lympha* adj2 (neoplasm* or malign* or tumor* or tumour* or sarcom*)).af.
15. (hemato* adj (malign* or neoplas*)).tw,kf,ot.
16. (haemato* adj (malign* or neoplas*)).tw,kf,ot.
17. or/10-16
18. 9 or 17
19. exp RADIOThERAPY/
20. (radiotherap* or radio-therap*).tw,ot.
21. exp LYMPHATIC IRRADIATION/
22. exp RADIOThERAPY, IMAGE-GUIDED/
23. exp RADIOThERAPY, COMPUTER-ASSISTED/
24. (radiotherap* or radiation* or irradiati*).tw,kf,ot.
25. or/19-24
26. 18 and 25
27. randomized controlled trial.pt.
28. controlled clinical trial.pt.
29. randomi?ed.ab.
30. placebo.ab.
31. clinical trials as topic.sh.
32. randomly.ab.
33. trial.ti.
34. or/27-33
35. humans.sh.
36. 34 and 35
37. 26 and 36
Appendix 3. CENTRAL search strategy

1. MeSH descriptor: [Lymphoma] explode all trees
2. MeSH descriptor: [Hematologic Neoplasms] explode all trees
3. MeSH descriptor: [Hematologic Malignancies] explode all trees
4. (lymphom* or linfom*)
5. (non-hodgkin* or non Hodgkin* or non-hodgkin* or non Hodgkin* or nonhogkin* or no Hodgkin* or non-hodkin* or non hodkin* or non hodkin* or non-hodgin* or non hodgin* or nonhodgin* or no hodgin* or non-hodgin* or non hodgin* or nonhodgin* or no hodgin* or nhl*)
6. (hemato* near/5 neoplas*) or (hemato* near/5 malign*) or (haemato* near/5 neoplasm*) or (haemato* near/5 malign*)
7. (bcell*) or (b*cell*)
8. #1 or #2 or #3 or #4 or #5 or #6 or #7
9. (lymph* adj2 sarcom*)
10. lymphosarcom*
11. (reticulum adj2 sarcom*)
12. (lymphom* adj2 (cleaved* or noncleaved* or grad* or mixed-cell* or pleomorphic* or diffus*))
13. (lympho* adj2 (neoplasm* or malign* or tumor* or tumour* or sarcom*))
14. (lympha* adj2 (neoplasm* or malign* or tumor* or tumour* or sarcom*))
15. #9 or #10 or #11 or #12 or #13 or #14
16. #8 or #15
17. MeSH descriptor: [Radiotherapy] explode all trees
18. MeSH descriptor: [Radiotherapy, Image-Guided] explode all trees
19. MeSH descriptor: [Radiotherapy, Computer-Assisted] explode all trees
20. MeSH descriptor: [Lymphatic Irradiation] explode all trees
21. (radiotherap* or radio-therap*)
22. (radiation therap*)
23. (Irradiati*)
24. #17 or #18 or #19 or #20 or #21 or #22 or #23
25. #16 and #24
CONTRIBUTIONS OF AUTHORS

EY is the co-ordinator of the review, guided by SFAW.
EY is responsible for data collection and organising retrieval of papers.
EY and ZKL are responsible for constructing the search strategy and undertaking searches.
EY, ZKL and SFAW are responsible for screening search results and appraising the risk of bias of studies.
All review authors will participate in analysis and interpretation of data.
EY is responsible for writing the review.

DECLARATIONS OF INTEREST

None known.

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- Universiti Kebangsaan Malaysia, Malaysia.
All authors are employees of the university

External sources
- No sources of support supplied