

## 8. Lymphoma

### Hodgkin lymphoma

#### Background

Over the last 30 years, combination chemotherapy has become integral to the standard of care for both early and late stage Hodgkin lymphoma. Previous techniques employing the traditional mantle and inverted Y fields are no longer practiced. Involved field radiotherapy (IFRT), which has been the standard until recently, is being replaced by involved node radiotherapy (INRT) or involved-site radiotherapy (ISRT), further reducing the treated volume for consolidation or residual disease after chemotherapy.<sup>1,2</sup> There should be every effort to reduce cardiac and lung doses when treating the mediastinum with good evidence to support the use of intensity-modulated radiotherapy (IMRT) and deep inspiration breath hold (DIBH) in this setting.<sup>3</sup>

#### Early Hodgkin lymphoma

Studies by the German Hodgkin Disease Study Group have shown no difference in outcome between two cycles of Adriamycin bleomycin vinblastine dacarbazine (ABVD) and 20 Gray (Gy) in ten fraction IFRT in the favourable subgroup or four cycles of ABVD and 30 Gy IFRT in the unfavourable subgroup (Level 1b).<sup>4-6</sup> Radiotherapy after chemotherapy in PET-negative patients reduces the later risk of relapse, but the absolute reduction in progression-free survival (PFS) was only 4% at three years in the RAPID trial (Level 1b).<sup>8,7</sup>

#### Recommendations

##### For patients with early Hodgkin lymphoma:

**Favourable group:** 2 cycles of ABVD chemotherapy followed by 20 Gy in 10 fractions over 2 weeks (Grade A)

**Unfavourable group:** 4 cycles of ABVD followed by 30 Gy in 15 fractions over 3 weeks (Grade A)

For selected patients who are PET negative after three cycles of ABVD, the relative risks of relapse from omitting radiotherapy and the late toxicity from giving radiotherapy should be considered and discussed with the patient (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

#### Advanced Hodgkin lymphoma

The role of radiotherapy in advanced Hodgkin disease after full-dose combination chemotherapy is controversial. One overview showed that combined-modality therapy conferred no survival benefit but did increase the risk of long-term fatal complications (cardiac and second cancer), while another, using UK National Cancer Research Institute (NCRI) study data, has shown an improved survival in patients with Hodgkin lymphoma who received radiotherapy compared to those who did not (Level 1a).<sup>6,8,9</sup> A European Organisation for Research and Treatment of Cancer (EORTC) study demonstrated that radiotherapy did not improve the outcome for patients who had a complete remission after mustine, vincristine, procarbazine, prednisolone-adriamycin bleomycin vinblastine (MOPP-ABV) chemotherapy, but that irradiation may benefit patients with a partial response after

chemotherapy (Level 1b).<sup>5,9</sup>

#### Recommendation

In advanced Hodgkin lymphoma, radiotherapy for residual disease is indicated after partial response to chemotherapy.

30–34 Gy in 15–20 fractions over 3 to 4 weeks (Grade B)

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#### Relapsed Hodgkin lymphoma

High-dose chemotherapy and stem cell transplantation remain the international standard of care for many younger patients with relapsed Hodgkin lymphoma.

In some patients with a single site of relapse, particularly occurring late, after previous treatment, re-induction as for early disease combined with IFRT may be appropriate, using a dose of 30–34 Gy in 15–20 fractions over 3–4 weeks.

If the site has not previously been irradiated, radiotherapy alone has been used for selected patients (Grade D).<sup>6,11</sup>

#### Recommendations

For palliative treatments no definitive recommendations can be made and dose will depend on the clinical situation. The following may be used:

30 Gy in 10 fractions over 2 weeks (Grade D)

20 Gy in 5 fractions over 1 week (Grade D)

Single doses of 7–8 Gy (Grade D)

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#### Nodular lymphocyte Hodgkin lymphoma

IFRT alone, without chemotherapy, results in high PFS and overall survival (OS) rates and is considered an adequate treatment for early stage disease.<sup>12</sup> A dose of 30 Gy in 15 fractions over three weeks is recommended (Grade D).<sup>6</sup>

#### Aggressive non-Hodgkin lymphoma (NHL)

In aggressive lymphomas, radiotherapy alone is not recommended except in palliative situations or where the patient is too frail for chemotherapy.

#### Consolidation IFRT in aggressive non-Hodgkin lymphoma

Following the landmark study comparing eight cycles of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy to three cycles of CHOP followed by IFRT with 40–45 Gy in 1.8–2 Gy fractions, combined modality therapy was established as the standard of care.<sup>13</sup> Longer term follow-up has shown convergence of the survival

curves, as a result of an excess of relapses and deaths from lymphoma in the group given CHOP plus radiotherapy (Level 1b).<sup>14,6</sup> In a further study, patients who received eight cycles of CHOP chemotherapy and achieved complete remission, 30 Gy in daily 2 Gy fractions improved local control (Level 1b).<sup>15,16</sup> A further trial in patients aged <61 years with no adverse prognostic factors has shown improved event-free and overall survival rates with doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (ACVBP) chemotherapy over those achieved by CHOP plus IFRT (Level 1b).<sup>6,16</sup>

There are therefore two treatment approaches to the patient with early aggressive NHL: short-course immunochemotherapy rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) followed by IFRT or full-course R-CHOP with six to eight cycles alone. The relative merits should be discussed with the patient. There is no evidence to suggest that early PET response can be used to individualise treatment the schedule at present.

Recent evidence from the rituximab with CHOP over age 60 years (RICOVER) trial suggests that there may be a role for radiotherapy in advanced stage diffuse large B-cell lymphoma (DLBCL) given to bulky sites of disease at presentation after chemotherapy (Level 2b).<sup>6,17</sup>

Radiotherapy is also considered for mediastinal B-cell lymphoma and extranodal sites after full-course chemotherapy.<sup>18</sup>

A randomised trial of radiotherapy dose comparing 30 Gy to 40–45 Gy (all in daily two Gy fractions) has demonstrated that in aggressive NHL 30 Gy is equivalent to a higher dose for local PFS and OS. All patients with aggressive NHL receiving radiotherapy should therefore be given 30 Gy in 15 fractions over three weeks (Level 1b).<sup>6,19</sup>

### Recommendation

#### **For patients with aggressive non-Hodgkin lymphoma:**

30 Gy in 15 fractions over 3 weeks is recommended as part of planned combined modality therapy (Grade B).

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### Mantle cell lymphoma

This disease has a poor prognosis. The vast majority of patients require systemic treatment, although the standard of care is not yet established. In combined modality treatment, there is no evidence that mantle cell lymphomas respond differently to radiation compared to other aggressive lymphomas. A recent retrospective multi-institutional study of stage 1–2 patients reported favourable outcomes with combined modality or radiotherapy alone with two-thirds and half of the patients being free of disease at five and ten years respectively. Median dose was 35 Gy (range 12–45 Gy) (Grade C).<sup>6,20</sup>

## Natural killer (NK)/T-cell lymphoma

This is a rare entity in Western countries but is common in East Asia and Latin America.<sup>20</sup> Chemoradiation using cisplatin-based schedules and l-asparaginase are now standard, followed by consolidation chemotherapy. This type of lymphoma requires a higher dose than other T-cell lymphomas and a dose of at least 50 Gy in 25 fractions over five weeks should be given (Grade C).<sup>6,22</sup>

## Central nervous system lymphoma (CNS) lymphoma

The role of radiotherapy in CNS lymphoma is controversial in view of the significant late effects on cognitive function. It may be indicated after chemotherapy, particularly where there is an incomplete response and also in relapsed disease. Standard lymphoma doses are considered inadequate in the CNS and recommended doses would be 40–45 Gy in 20–25 fractions over four to five weeks (Grade C).<sup>6,23</sup>

## Mycosis fungoides

This will typically be a widespread skin infiltration with radiotherapy used for palliation of thicker plaques. Doses of 8 Gy in two fractions or 12 Gy in three fractions are recommended (Grade C).<sup>6,24</sup>

## Indolent lymphoma

Indolent lymphoma includes follicular lymphoma, small lymphocytic lymphoma and marginal zone lymphoma. Stage I indolent lymphoma has, for many years, been treated with radical IFRT. In advanced stage indolent lymphoma, IFRT may be indicated for control of local symptomatic disease.

A randomised trial comparing 24 Gy to 40 Gy (all in 2 Gy fractions) included patients with early stage indolent lymphoma. There was no difference in local PFS or OS between these two dose arms. A subsequent study randomised patients with follicular and marginal zone lymphoma to receive either 24 Gy in 12 fractions or 4 Gy in two fractions. At 12 weeks, the complete response rate was 68% after 24 Gy and 49% after 4 Gy. Local PFS was also strongly in favour of the 24 Gy arm with a hazard ratio for local progression of 3.42 (95% confidence interval [CI]: 2.10–5.57). Toxicity was low in both arms (Level 1b).<sup>6,25</sup>

### Recommendation

#### **For the radical treatment of stage I, indolent lymphoma, or durable palliation in more advanced stages:**

24 Gy in 12 fractions over 2.5 weeks (Grade B)

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## Palliative treatment of non-Hodgkin lymphoma

In patients with follicular lymphoma, high response rates have been achieved after low-dose IFRT (4 Gy in 1 or 2 fractions), however, the randomised trial comparing 4 Gy to 24 Gy showed that, while effective in many patients, 4 Gy was inferior for local control (Level 1b).<sup>6,25,26</sup> Where short-term palliation is the aim of treatment, 4 Gy in 2 fractions may be considered.

For aggressive lymphoma, a single dose of 8 Gy or short-course palliation such as 20 Gy in five fractions or 30 Gy in ten fractions are effective and appropriate for the palliative treatment of many patients with a limited prognosis (Grade D).<sup>6</sup>

### Recommendations

**In the palliative management of lymphoma, there is evidence to support the following regimens:**

#### **Indolent lymphoma:**

24 Gy in daily 2 Gy fractions over 2.5 weeks (Grade A)

#### **For short-term palliation in follicular or marginal zone lymphoma:**

4 Gy in 2 fractions (Grade A)

#### **Intermediate/high-grade lymphoma:**

Single dose 8–10 Gy (Grade D)

20 Gy in 5 fractions over 1 week (Grade D)

30 Gy in 10 fractions over 2 weeks (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

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