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Hodgkin lymphoma

Background

Over the past 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 practised. Involved-field radiotherapy (IFRT) has been replaced by involved-node radiotherapy (INRT) or involved-site radiotherapy (ISRT), further reducing the treated volume for consolidation or residual disease after chemotherapy.[1,2] 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.[3,4]

Early Hodgkin lymphoma

The HD-10 study by the German Hodgkin Study Group (GHSG) showed no difference in outcome in the favourable subgroup (stages I–II without risk factors) between two cycles of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) and 20 Gray (Gy) in 10 fractions IFRT or four cycles of ABVD and 30 Gy IFRT (Level 1b).[5–6] In early unfavourable disease, the GHSG HD-11 study established 4 cycles of ABVD and 30 Gy as the best arm.[7]

Subsequently, three large randomised controlled trials (RCTs)[8–10] testing the omission of radiotherapy in patients achieving complete metabolic response (CMR) on interim positron emission tomography (PET) scanning showed that the omission of radiotherapy results in increased relapse rates when ABVD chemotherapy is used.

One study in early-stage unfavourable (stages I–II with risk factors) Hodgkin lymphoma using a 2+2 approach (escalated BEACOPP × 2 + ABVD × 2) showed that the omission of radiotherapy in patients achieving CMR after all chemotherapy was not inferior in terms of 5-year progression-free survival (Level 1b).[6,11]

Combined modality treatment therefore remains to be the standard of care in ABVD-treated early-stage Hodgkin lymphoma but the decision on radiotherapy needs to be carefully considered on an individual patient basis, taking account of their age, sex, smoking history and the anatomical disease distribution, and weighing up predicted risks of late toxicity against potential benefit of improved disease control.[12,13]

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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 patients treated with escalated BEACOPP×2 + ABVD ×2, radiotherapy can be omitted if there is CMR on PET scanning after chemotherapy (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.[6]

Advanced Hodgkin lymphoma

The role of radiotherapy in advanced Hodgkin disease after full-dose combination chemotherapy is controversial and has changed with the introduction of PET imaging.

In the context of ABVD chemotherapy, two Italian RCTs[14,15] randomised patients with initial bulk disease (defined as >5 cm) who demonstrated CMR on both interim (post cycle 2) and end of treatment PET after 6 cycles to radiotherapy (30 Gy in 15 fractions) or no radiotherapy. The two studies showed no statistically significant benefit from consolidation radiotherapy to sites of initial bulk, although they were not powered adequately (Level 1b).[6] The outcomes of the chemotherapy alone arms were excellent, suggesting that any potential benefit from radiotherapy would be very small. The benefit of radiotherapy in patients with partial metabolic response and who continue on ABVD is unknown, as these patients were escalated to more intensive chemotherapy.

In the context of escalated BEACOPP chemotherapy, the GHSG HD-15 study[16] showed that patients achieving CMR do well without radiotherapy to sites of bulk, and patients who have residual fluorodeoxyglucose (FDG) uptake on PET may benefit from consolidation radiotherapy (30 Gy in 15 fractions) (Level 1b).[6]

Recommendation

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

- 30–36 Gy in 15–20 fractions over 3 to 4 weeks (Grade B)

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.[6]

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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 following previous combined modality treatment. Selected cases of early-stage disease, who relapse after previous chemotherapy alone treatment, may be successfully salvaged with radiotherapy.

The presence of residual PET-positive disease following salvage systemic treatment is an adverse prognostic factor for early relapse after stem cell transplant.[17] Radiotherapy to areas of persistent disease can be used to induce a better remission status. Dose will depend upon the patient's response to salvage systemic treatment and normal tissue constraints.[18]

In some patients with a single site of relapse, particularly occurring late, after previous treatment, reinduction as for early disease combined with ISRT may be appropriate, using a dose of 30–36 Gy in 15–20 fractions over 3–4 weeks (Grade D).[6,18]

Recommendations

In relapsed/refractory disease, the following may be used:

To consolidate complete response following systemic treatment:

- 30 Gy in 15 fractions over 3 weeks (Grade D)
- Persistent disease seen following systemic treatment:
- 36–40 Gy in 18–20 fractions over 3–4 weeks (Grade D)

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 dose of 8 Gy (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.[6]

Nodular lymphocyte-predominant Hodgkin lymphoma

ISRT alone, without chemotherapy, results in high progression-free survival (PFS) and overall survival (OS) rates and is considered an adequate treatment for early-stage disease.[19] A dose of 30 Gy in 15 fractions over 3 weeks is recommended (Grade D).[6,20]

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Aggressive non-Hodgkin lymphoma (NHL)

The most common subtype of aggressive NHL is diffuse large B-cell lymphoma (DLBCL). Radiotherapy has been used as part of combined modality treatment for localised disease or as a consolidation after chemoimmunotherapy in selected cases of advanced-stage disease, most commonly for bulky sites. Historical studies used radiotherapy doses of 40–45 Gy in DLBCL but the BNLI study, published in 2011, demonstrated that 30 Gy is equivalent to higher doses in aggressive NHL (Level 1b).[6,26]

Of note, the evidence for dose fractionation in aggressive NHL comes predominantly from data on DLBCL. However, less common subtypes, such as peripheral T-cell lymphomas, were also included in the BNLI study, albeit in much smaller numbers. The extrapolation of dose fractionation schedules from DLBCL to the other less common subtypes of aggressive NHL is therefore considered reasonable, given the limited data available for the rarer subtypes. An exception to this is NK/T-cell lymphoma (see separate section below).

Localised DLBCL

The standard of care is short-course chemotherapy (R-CHOP ×3) followed by ISRT, or alternatively 6 cycles of R-CHOP alone. The two options have similar oncological outcomes based on historical data.[21,22] However, they differ in their toxicity profile and choice may therefore depend on site of disease, age, sex and co-morbidities of patients and their preference.

More recently, selected cases with very good prognosis (age <60, IPI=0, no bulk) achieved a similar outcome with 4 cycles of R-CHOP and 2 additional cycles of rituximab without radiotherapy (Level 1b).[6,23]

Advanced DLBCL

In advanced-stage disease, the RICOVER-60 study showed a PFS and OS benefit for radiotherapy (36 Gy in 18 fractions) given to initial sites of bulk and extranodal disease after 6 cycles of R-CHOP-14 in patients with DLBCL aged >60 years (Level 1b).[6,24] In patients aged <60 years, the UNFOLDER RCT[25] (reported in abstract form only) showed a 16% benefit in 3-year event-free survival in those assigned to receive radiotherapy versus no radiotherapy (Level 2b).[7] Based on these studies, radiotherapy has been offered as consolidation for bulky sites after R-CHOP. However, it remains currently unknown if patients achieving CMR after R-CHOP still benefit from radiotherapy, and there are no randomised studies to answer this question.

Chemorefractory DLBCL

In patients with residual disease after chemotherapy, higher doses of 36–40 Gy in 2 Gy fractions should be considered (Level 2b).[27–29]

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Bridging to chimeric antigen receptors cell therapy (CAR-T)

CAR-T is an effective salvage treatment for relapsed or refractory DLBCL and primary mediastinal B-cell lymphoma. Radiotherapy has been used successfully as a bridging therapy to halt disease progression and maintain patient condition during the period of cell manufacture. Several small studies reported a range of doses and treatment duration, usually chosen depending on treatment site and to minimise delay of CAR-T infusion (Level 2b).[6,30]

Recommendations

For patients with DLBCL:

- In early-stage DLBCL, 30 Gy in 15 fractions over 3 weeks is recommended as part of combined modality treatment (Grade B)
- In patients with CMR receiving consolidation radiotherapy (eg to initial sites of bulk), a dose of 30 Gy in 15 fractions over 3 weeks is recommended (Grade B)
- In patients with incomplete response to systemic treatment, consider higher doses of 36 Gy–40 Gy in 18–20 fractions over 3–4 weeks (Grade C)
- Extrapolation of these dose recommendations to other less common subtypes of aggressive NHL is reasonable (with the exception of NK/T-cell lymphoma; see separate section below)

For bridging to CAR-T:

- 30 Gy in 10–15 fractions over 2–3 weeks or 20 Gy in 5 fractions over 1 week (Grade C)

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.[6]

Mantle cell lymphoma (MCL)

The vast majority of patients present with advanced disease and require systemic treatment. However, MCL is radiosensitive and responds well even to low doses of radiation, making radiotherapy a useful option for local control or palliation of specific disease sites. MCL less frequently presents as localised disease; radiotherapy alone has been used and is associated with reasonable outcomes. Doses in the range of 4–30 Gy can be used.[31–34]

Natural killer (NK)/T-cell lymphoma

This is a rare entity in Western countries but is common in East Asia and Latin America. 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 45–50 Gy in 25 fractions over 5 weeks should be given (Grade C).[6,35,36]

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Central nervous system lymphoma (CNS) lymphoma

The landmark IELSG32 trial[37] established the MATRIx chemo-immunotherapy schedule (methotrexate, cytarabine, thiotepa and rituximab) as a new standard of care in primary CNS lymphoma for fit patients (Level 1b).[6] Following systemic treatment, patients were consolidated with either autologous stem cell transplantation (ASCT) or whole-brain radiotherapy (36 Gy in 20 fractions over 4 weeks with additional 9 Gy in 5 fraction boost to tumour bed in cases of partial response). There was no significant difference in 2-year PFS (80% for WBRT) but neurocognitive deficit was noted in a subset of the WBRT cohort at 2-year follow-up (Level 1b).[6,38]

Escalation beyond 36 Gy to the whole brain in patients who have achieved a complete response following high-dose methotrexate-based chemotherapy has not been shown to offer additional clinical benefit (Level 2b)[6,39] but could increase neurotoxicity.

In view of the observed neurotoxicity seen with consolidation WBRT, the standard of care for primary CNS lymphoma is consolidation ASCT after MATRIx chemotherapy. In patients not fit for ASCT or those not responding to systemic treatment, radiotherapy may be used as consolidation or palliation. Dose choice will depend on patient fitness, age and predicted risk of neurotoxicity.

Of note, in patients with a complete response to rituximab, methotrexate, procarbazine and vincristine (R-MPV), a reduced dose of 23.4 Gy in 1.8 Gy fractions to the whole brain resulted in 2-year PFS of 77% with minimal neurotoxicity (Level 2b).[6,40]

Recommendations

- For patients with primary CNS lymphoma not fit for consolidation ASCT or those not responding to chemotherapy, consider consolidation WBRT with a dose of 23.4–36 Gy in 1.8 fractions (Grade B)
- In the palliative setting, consider 20 Gy in 5 fractions (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.[6]

Palliative treatment of aggressive non-Hodgkin lymphoma

For aggressive lymphoma, a single dose of 8 Gy or short-course palliation such as 20 Gy in 5 fractions or 30 Gy in 10 fractions are effective and appropriate for the palliative treatment of many patients with limited prognosis (Grade D.)[6]

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Recommendations

In the palliative management of aggressive non-Hodgkin lymphoma, the following are recommended:

- 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.[6]

Mycosis fungoides

This will typically be a widespread skin infiltration with radiotherapy used for palliation of thicker plaques. Doses of 8 Gy in 2 fractions or 12 Gy in 3 fractions are recommended (Grade C).[6,41]

Indolent lymphoma

Indolent lymphoma includes follicular lymphoma, marginal zone lymphoma (including extranodal marginal zone lymphoma, MALT), small lymphocytic lymphoma, lymphoplasmacytic lymphoma and other rarer types. Stage I indolent lymphoma has, for many years, been treated with radical radiotherapy. In advanced-stage indolent lymphoma, radiotherapy may be indicated for control of local symptomatic disease.

A randomised trial comparing 24 Gy with 40 Gy (all in 2 Gy fractions) included patients with early-stage indolent lymphoma.[26] There was no difference in local PFS or OS between these two dose arms (Level 1b).[6] A subsequent study[42] randomised patients with follicular and marginal zone lymphoma to receive either 24 Gy in 12 fractions or 4 Gy in 2 fractions.

At 12 weeks, the complete response rate was 68% after 24 Gy and 49% after 4 Gy. Toxicity was low in both arms (Level 1b).[6] PFS at 5 years was reported as 89.9% with 24 Gy and 70.4% with 4 Gy,[43] establishing 24 Gy as the standard dose for definitive radiotherapy (Level 1b).[6] However, 4 Gy remains a useful alternative in selected cases for palliation, providing good outcomes with low toxicity and more patient convenience.

Recommendations

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 A)
- 4 Gy in 2 fractions is an alternative option for palliation (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.[6]

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