Clinical Oncology 25 (2013) 11–18

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

The Management of Children with Lymphomas

J.A. Frew, J. Lewis, H.H. Lucraft

Northern Centre for Cancer Care, The Freeman Hospital, High Heaton, Newcastle-upon-Tyne, UK

Received 17 July 2012; received in revised form 10 August 2012; accepted 13 August 2012

Abstract

Lymphomas account for 10–15% of all paediatric malignancies. They are highly curable with 5 year survival rates of up to 95% for Hodgkin lymphoma and 82% for non-Hodgkin lymphoma. These excellent results have focused recent attention on reducing the burden of treatment-related morbidity while maintaining the excellent outcomes. Lymphomas are highly radiosensitive and radiotherapy was used historically in the treatment of both paediatric Hodgkin and non-Hodgkin lymphomas. As the late effects of radiotherapy, including second tumours, were recognised, successive protocols seeking to minimise late effects were developed that reduced the use of radiotherapy. Current treatment protocols for non-Hodgkin lymphoma are chemotherapy based and radiotherapy has been virtually eliminated. In contrast, current paediatric Hodgkin lymphoma protocols continue to use radiotherapy as part of combined modality treatment, targeted according to risk factors and response and at the minimum effective dose. This article reviews the treatment of Hodgkin lymphoma in children with particular emphasis on the role of radiotherapy.

Key words: Chemotherapy; Hodgkin; late effects; paediatric lymphoma; radiotherapy

Statement of Search Strategies Used and Sources of Information

This review was based on a literature search on Medline, Embase and the Cochrane library through NHS Evidence, last accessed 17 February 2012. The thesaurus terms used were: Hodgkin disease, lymphoma, radiotherapy, child for Medline and Hodgkin disease (limited to radiotherapy and child) for Embase.

Introduction

Hodgkin lymphoma (HL) is a highly curable malignancy with 5 year survival rates of up to 95% [1]. The presenting symptoms in children are similar to those in adults, with painless supradiaphragmatic lymphadenopathy and non-specific systemic symptoms being most common. It is highly radiosensitive and radiotherapy was used historically as the mainstay of treatment. The World Health Organization classification of lymphomas divides HL into classical HL and non-classical nodular lymphocyte predominant HL (NLPHL).

Non-classical NLPHL is considered a distinct histological entity characterised by CD20-positive lymphocytic and histiocytic Reed–Sternberg cell variants (popcorn cells). It has a different natural history to classical HL [2,3] with some similarities to low-grade non-Hodgkin lymphoma (NHL). Involved-field radiotherapy (IFRT) is an effective treatment for localised NLPHL, but is usually avoided in children to minimise late effects. Patients with early stage disease (IA and IIA) are currently being recruited into a European trial investigating surgery alone, where possible, or low-dose chemotherapy using CVP (a summary of chemotherapy regimens used in paediatric HL is found in Table 1).

Classical HL occurs more commonly (90–95% of cases) and is the main subject of this article. It is subdivided into four subtypes (nodular sclerosing, mixed cellularity, lymphocyte-rich and lymphocyte-depleted), which do not influence treatment decisions. As in adults, nodular sclerosis is the most common form of paediatric HL. Until the 1960s, the management of HL was palliative using orthovoltage radiotherapy to obtain local control. During the 1960s, surgical staging and extended-field radiotherapy

Author for correspondence: J.A. Frew, Northern Centre for Cancer Care, The Freeman Hospital, High Heaton, Newcastle-upon-Tyne NE7 7DN, UK. Tel: +44-191-2336161; Fax: +44-191-2137697.

E-mail address: john.frew@nuth.nhs.uk (J.A. Frew).

0936-6555/$36.00
http://dx.doi.org/10.1016/j.clon.2012.09.009

Table 1
Chemotherapy regimens, cycle duration and drug components

Chemotherapy regimen	Cycle duration (days)	Drug components
ChlVPP	28	Chlorambucil, vinblastine, procarbazine, prednisolone
ABVD	28	Doxorubicin, bleomycin, vincristine, dacarbazine
EPIC	21	Etoposide, prednisolone, ifosfamide, cisplatin
OPPA	28	Doxorubicin, vincristine, procarbazine, prednisolone
OEPA	28	Doxorubicin, vincristine, etoposide, prednisolone
COPP	28	Cyclophosphamide, vincristine, procarbazine, prednisolone
VAMP	28	Vinblastine, doxorubicin, methotrexate, prednisolone
COPDAC	28	Cyclophosphamide, vincristine, prednisolone, dacarbazine
IEP-ABVD	50	Ifosfamide, etoposide, prednisolone - doxorubicin, bleomycin, vinblastine, dacarbazine

(EFRT) offered the chance of cure for the first time to patients with localised disease (stage I–III). The high response rates to various cytotoxic drugs was recognised by the early 1970s, with combination chemotherapy regimens achieving complete remission rates in advanced HL (stage IIIB/IV) of around 50%. The standard of care at this time was EFRT for localised HL and intensive multi-agent chemotherapy with the addition of radiotherapy in advanced disease. The success of these treatment strategies was accompanied by significant morbidity in children. EFRT was delivered at a dose of 40–44 Gy over 4–5 weeks. This resulted in retardation of skeletal and soft tissue development [4,5], ovarian failure after pelvic radiotherapy [6], endocrine deficiencies including hypothyroidism [7], late coronary artery disease [8,9] and secondary solid tumours, arising predominantly within the irradiated fields [10,11].

International research groups have carried out successive generations of clinical trials in paediatric HL. Chemotherapy regimens have evolved to minimise late effects, including reducing the use of alkylating agents and procarbazine to reduce the risk of second malignancies and infertility. These trials have refined the indications for radiotherapy as well as progressively reducing dose and target volumes. EFRT is no longer used, with a shift towards IFRT and more recently modified IFRT (mIFRT) to minimise the treatment volume (Figure 1). Radiotherapy, in current paediatric HL protocols, is part of combined modality treatment, targeted according to risk factors and response and at the minimum effective dose. Biological markers of risk are, so far, disappointing. Clinical stage and speed of response as measured by anatomical response and functional imaging by early interim [18F]fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning are strong prognostic factors and are currently being assessed as determinants of treatment policies.

Overview of Paediatric Hodgkin Lymphoma Trials

United Kingdom Children's Cancer Study Group (UKCCSG)/ Children's Cancer and Leukaemia Group (CCLG)

The experience within the UK is derived from three successive trials carried out by the United Kingdom Children's Cancer Study Group (UKCCSG) now known as the Children's Cancer and Leukaemia Group (CCLG). These studies have focused on single modality treatment for all stages of disease to limit the toxicity of combined chemotherapy and radiotherapy. In the UK HD82 trial, stage I patients with disease confined to the neck were treated with primary IFRT, which resulted in good overall survival rates in excess of 90% [12]. However, 30% of patients required salvage chemotherapy, which resulted in significant additional toxicity. The HD2000/02 trial advocated parental input in choosing between primary chemotherapy and radiotherapy for stage I patients after discussing the differing side-effect profiles. This resulted in most children being treated with primary chemotherapy. Primary chemotherapy for patients with stage II–IV disease has been the mainstay of treatment within all the UKCCSG trials.

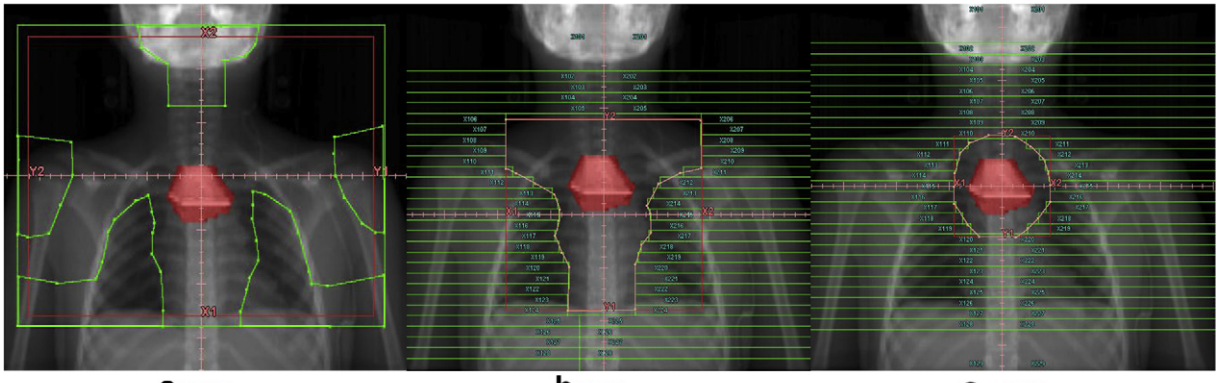

Fig 1. Beam's eye view images showing (a) extended-field radiotherapy (EFRT), (b) involved-field radiotherapy (IFRT) and (c) modified IFRT (mIFRT) techniques. Involved lymph nodes are outlined in red.