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Review

Treatment of paediatric Hodgkin's disease: a balance of risks

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Abstract

Hodgkin's disease is one of the commoner malignancies presenting in adolescence and young adulthood and is curable in the majority of cases. A number of therapeutic regimens have been used successfully, often at the expense of the development of side-effects in later life, including second malignancies, infertility and cardiac disease. We discuss the challenge faced by paediatric oncologists today in finding the balance between maximising cure and minimising the late effects. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Hodgkin's disease; Childhood; Treatment; Survival; Cure; Late effects

1. Introduction

With current overall survival for paediatric Hodgkin's disease in excess of 90% in low stage disease and 69% for disseminated disease, the late effects of treatment are assuming greater importance. Impaired growth of soft tissues and bone after spinal irradiation, and thyroid dysfunction following radiotherapy to the neck are well documented [1,2]. Subfertility following alkylating agent-based regimens is almost universal in males, and premature ovarian dysfunction is reported in a substantial number of females [3,4]. Both cardiopulmonary disease and second malignancies are also reported in a significant number of patients following treatment for childhood Hodgkin's disease [5,6].

The challenge for oncologists today is to minimise late toxicity without compromising the excellent survival rates. Over the last decade, combined modality therapy has enabled a reduction in the dose and size of the radiotherapy field, while also permitting a reduction in the cumulative dose of cytotoxic agents. The optimal chemotherapy regimen is subject to ongoing national and international studies. We review the current treatment strategies available for the management of paediatric Hodgkin's disease and discuss the relative risks and benefits associated with these regimens.

2. Epidemiology

Ten percent of Hodgkin's disease occurs in childhood, with an incidence of 3.6 per million children per year in the UK. The incidence is highest in late childhood and early adulthood, very uncommon under 5 years of age and almost never seen under 2 years of age. In developing countries, children under 5 years of age are more commonly diagnosed, perhaps reflecting the higher prevalence of Epstein–Barr Virus (EBV). The sex ratio progresses from one of male preponderance of 10:1 under the age of 7 years, falling to 1.1:1 after the age of 12 years [7,8].

3. Presentation

The most frequent presentation in up to 80% of patients is painless cervical lymphadenopathy, of whom up to 60% have asymptomatic involvement of the mediastinum. Constitutional or 'B' symptoms (night sweats, unexplained fever or weight loss) are more likely to be present with higher stage disease (stage I, 5%, stage IV 81%) and are associated with a poorer outcome [8].

4. Staging

The stage of the disease is assigned according to the Ann Arbor staging classification and accurate staging of

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the disease is essential for treatment planning [9]. In the past, laparotomy and splenectomy were necessary for accurate staging and pathological verification of the extent of the disease [10]. Studies have failed to show any superiority for surgical staging compared with radiological staging before treatment with combined modality therapy [11]. Elimination of staging by laparotomy and splenectomy has led to an important reduction in deaths from surgically-related complications and overwhelming, predominantly pneumococcal, infections.

With mediastinal involvement in up to 60% of cases, accurate thoracic imaging with computed tomography (CT) or magnetic resonance (MR) is essential. Gallium scanning, with a lower false-positive rate than CT scanning, is also a useful tool for assessing thoracic disease and therapy response [12]. Lymphangiography is an excellent method for assessing abdominal lymph node involvement, but has largely been superseded by CT and MR imaging which are easier and less invasive procedures. Ultrasound is also a useful tool for abdominal lymph node assessment in children, and in addition, enables determination of splenic size and hepatic involvement [13–15].

Laboratory investigations will include a full blood count and often erythrocyte sedimentation rate (ESR). Lymphopenia is a sign of advanced disease and an elevated ESR correlates closely with disease stage and the presence of systemic symptoms. Although bone marrow involvement is reported to be as infrequent as 3%, bone marrow biopsies should be performed in patients with advanced disease, systemic symptoms, bony involvement or abnormal blood count. MR imaging may provide a valuable alternative non-invasive means of evaluating marrow involvement [16].

5. Current treatment strategies

5.1. Low stage disease (stages I and IIA [9])

Over the last 40 years, there has been a steady evolution in the management of Hodgkin's disease with continual refinement of both radiotherapy and chemotherapy regimens to reduce both mortality and morbidity. Treatment strategies for paediatric Hodgkin's disease consist of either combined modality therapy, which enables considerable reduction in the dose intensity and field of irradiation, and a reduction in the cumulative dose of cytotoxic chemotherapy, or chemotherapy alone [14,15,17,18]. So-called 'hybrid' protocols, in which two different chemotherapy regimens are alternated, are another method used to reduce 'late sequelae' [19,20]. Although hybrid combination chemotherapy will expose the child to a wider variety of drugs, it is expected that the total cumulative dose of any individual agent will decrease the prevalence of unwanted long-term side-effects. The chemotherapy regimens involve several courses of four cytotoxic drugs in combination or in cyclical 'hybrid' combination. The types of regimens used by most international study groups are alkylating agent-based (MOPP (mechlorethamine + vincristine + procarbazine + prednisolone), ChlVPP (chlorambucil + vinblastine + procarbazine + prednisolone) or COPP (cyclophosphamide + vincristine + procarbazine + prednisolone)), anthracycline-based (ABVD (doxorubicin + bleomycin + vinblastine + dacarbazine) or OPPA (vincristine + procarbazine + prednisolone + doxorubicin)) and epipodophyllotoxin-based (VEEP (vincristine + etoposide + epirubicin + prednisolone) or OEPA (vincristine + etoposide + prednisolone + doxorubicin)). In some protocols, radiotherapy at a total dose of 35 Gy (Gray) is given alone for early stage disease [21], whilst a total dose limited to 15–35 Gy, restricted to involved fields, is administered as 'consolidation' radiotherapy. Overall 5-year survival rates are in excess of 90% for low stage disease regardless of the chosen regimen (93–100%), but greater differences are observed in the 5-year event-free survival rates, which range from 70 to 100% (Table 1) [20–40]. The most striking observation is the high relapse rate of 30% seen in the UK stage I patients treated with radiotherapy alone [21]. Most of the patients who relapsed had mixed cellularity histology, which may represent a more aggressive pathological subgroup.

5.2. Bulky and higher stage disease (stage IIB–IV [9])

Modern treatment strategies yield cure rates of 69–96% for children with bulky or high stage Hodgkin's disease (Table 1) [20–40]. These patients have received more intensive therapy and understandably have a greater risk of developing therapy-related late effects. The challenge in these patients is to develop therapeutic strategies to enhance the rate of cure, but lessen the long-term morbidity. As with early stage disease, there is a shift towards the use of hybrid chemotherapy protocols in an attempt to reduce late toxicity. Some 'hybrid' chemotherapy protocols give higher cure rates than single regimen therapy, although data is limited in children. In adults, a rondomised control trial demonstrated that 6–10 courses of alternating ABVD/MOPP were more effective than MOPP alone [37]. In the UK, treatment for stage IV disease has customarily involved 6–10 courses of ChlVPP, with consolidation radiotherapy (35 Gy) given to children with bulky mediastinal disease. However, while the 10-year overall survival rate of 71% is similar to results from other groups the progression-free survival rate (PFS) of 38% does not compare favourably with other reported international studies [10]. Current management in the UK of high stage disease is with hybrid chemotherapy regimens (ChlVPP/ABVD) with poor responders receiving EPIC (etoposide + prednisolone + ifosfamide + cisplatin) [39].

Table 1
Survival and event-free survival by stage and treatment for paediatric Hodgkin's disease

Study	Patients	Dates	Staging	Therapy	5 year OS (%)		5 year EFS/PFS (%)	
DAL HD90 [27]	578	1990–1995	I–IIA	OPPA or OEPA×2 plus 25 Gy				
			IIB–IIIA	OPPA or OEPA×2, COPP×2 plus 25 Gy	98		91	
			IIIB–IV	OPPA or OEPA×2, COPP×4 plus 20 Gy				
Hudson [25]	85	1980–1990	I	COP×5/ABVD×4 plus 15–25 Gy	90			
			II	Plus CO during radiotherapy	100 (93)		93	
			IV		86			
POG [30]	179	1987–1992	IIB–IVB	MOPP/ABVD×8	96		79	
				MOPP/ABVD×8 plus 10.5–21 Gy	87		80	
Stanford [20]	57	1982–1990	I–IV	ABVD/MOPP×6 plus 15 Gy	93		96	
			I–III		100	(10 year)	100	(10 year)
			IV only		69		85	
Ped HD1 [24]	55	1971–1983	I–IV	MOPP×6 plus 15–25 Gy	89	(10 year)	90	(10 year)
UKCCSG [21]	331	1982–1992	I	Localised radiotherapy only (35 Gy)	92		70	
			II	ChlVPP×6–10 plus 35 Gy for bulky	92	(10 year)	85	(10 year)
			III	mediastinal disease all stages other than IA	84		73	
			IV		71		38	
Shankar [40]	54	1987–1995	I–III	VEEP×6–8	93		82	
			IV	Plus 35 Gy for bulky mediastinal disease	44		50	
MDH 90 [32]	202	1990–1996	I	VBVP×4 plus 20 Gy (good responders)	99		91	
			II	VBVP×4 plus OPPA×1–2 plus 20–40 Gy	96		78	
Ekert [29]	53	1978–1982	I–IV	MOPP×6 or ChIVPP×6	94		92	
CCG 521 [38]	111	1986–1990	III–IV	ABVD plus 21 Gy (EF) versus	90		87	
				MOPP/ABVD	84		77	

OS, overall survival; EFS, event-free survival; PFS, progression-free survival; EF, extended field. Selection: Medline search for all studies on treatment of Paediatric Hodgkin's disease with greater than 50 patients. ABVD, doxrubicin + bleomycin + vinblastine + dacarbazine; ChlVPP, chlorambucil + vinblastine + procarbazine + prednisolone; COP, cyclophosphamide + vincristine + procarbazine; COPP, cyclophosphamide + vincristine + procarbazine + prednisolone; MOPP, mechlorethamine + vincristine + procarbazine + prednisolone; OEPA, vincristine + etoposide + prednisolone + doxorubicin; OPPA, vincristine + procarbazine + prednisolone + doxorubicin; VBVP, vinblastine + bleomycin + etoposide + prednisolone; VEEP, vincristine + etoposide + epirubicin + prednisolone; Gy, Gray (unit of radiation);

Institutions: DAL HD90: German–Austrian multicentre trial; Hudson: St Judes Children's Research Hospital, Memphis; POG: Roswell Park Memorial Institute Pediatric Oncology Group study; Ped HD1: Stanford study; UKCCSG: United Kingdom Children's Cancer Study Group; Shankar: UK and Repiblic of Ireland; MDH 90: French Society of Pediatric Oncology study; Ekert: Australia; CCG-521: Children's Cancer Group, North America.

VEEP, with or without involved field radiotherapy, is effective treatment in patients with stage I–IIIA, non-bulky disease, (5 year OS (overall survival) 93% and PFS 82%), but is inadequate alone in stage IV disease, bulky mediastinal disease, or the presence of B symptoms [40].

6. Late effects

Successful treatment of paediatric Hodgkin's disease using chemotherapy, radiotherapy, or both, is associated with late sequelae in a significant proportion of patients. Unwanted side-effects of treatment depend on the chemotherapy regimen and number of cycles, and the field and total dose of irradiation received. Late effects include infertility, cardiac disease, thyroid dysfunction, impaired growth of bone and soft tissues and the development of second malignancies. Cardiac toxicity and second malignancies account for two-thirds of fatalities amongst patients with Hodgkin's disease other than death due to the disease itself [41].

6.1. Thyroid dysfunction

Thyroid abnormalities are commonly encountered following neck irradiation and may present as hormonal dysfunction, thyroid nodules, including thyroid cancer [42–44]. Treatment for Hodgkin's disease with 30–50 Gy neck irradiation in fractionated doses results in overt hypothyroidism in 25% of patients, and many of the remainder have compensated biochemical hypothyroidism [1]. Thyroid carcinoma is fortunately rare with only 4 cases reported in a long-term follow-up study of 979 children [42]. However, it has been suggested that even doses to the thyroid gland as low as 0.09 Gy are associated with an increased risk of cancer [45].

6.2. Growth impairment

Growth retardation associated with spinal irradiation results from fractionated doses of 25–35 Gy, as a consequence of disruption within the growth plate, with more detrimental effects seen the younger the child at the time of treatment [46]. Irradiation to the neck may

result in poor growth of the neck, while soft-tissue fibrosis may result in lymphoedema of the limb, both of which may create cosmetic problems for the patient.

6.3. Fertility

6.3.1. Males

6.3.1.1. Radiotherapy. The testis is very sensitive to the gonadotoxic effects of both radiotherapy and chemotherapy. The nature of testicular damage depends on the field of treatment, total dose and fractionation schedule [3,47,48]. Radiotherapy causes azoospermia through direct damage to the germ cells and patients receiving greater than 1.2 Gy to the testes are likely to be rendered azoospermic, while smaller doses may damage dividing spermatogonia and disrupt cell morphology resulting in oligozoospermia [48,49]. Impaired androgen production, because of damage to the Leydig cells, results from higher doses and the degree of damage is dose- and age-dependent with the younger patient appearing to be more vulnerable (Table 2) [50].

6.3.1.2. Chemotherapy. Chemotherapy treatment of Hodgkin's disease with MOPP, ChlVPP and COPP has been reported in a number of studies to result in permanent azoospermia in more than 90%. The prepubertal testis appears to be as susceptible as the adult testis [51–53]. The gonadotoxic agents in these regimens are mechlorethamine and procarbazine in MOPP, chlorambucil and procarbazine in ChlVPP and procarbazine and cyclophosphamide in COPP [53,54]. The ABVD combination, which contains neither an alkylating agent or procarbazine, has been shown to be significantly less gonadotoxic, resulting in temporary azoospermia in 33% of patients and oligozoospermia in 21%, with 'full' recovery after 18 months reported in most, if not all, patients [54].

'Hybrid' regimens (e.g. three cycles of ABVD with three cycles of ChlVPP or MOPP) are likely to be less gonadotoxic. Fertility seems to be preserved in approximately 50% of men following three cycles of MOPP/ABVD, in contrast to almost universal azoospermia following six cycles of MOPP [55]. German–Austrian studies have shown that replacing the two 'OPPA' induction cycles with OEPA in the highly efficacious OPPA/COPP combined modality regimen reduces therapy related testicular dysfunction and maintains excellent 5-year event-free survival/overall survival rates of 91%/98% [27].

6.3.2. Females—ovary

6.3.2.1. Radiotherapy. Female fertility may be compromised following radiotherapy or chemotherapy treatment for childhood cancer. Damage to the ovary may be a consequence of total body, abdominal or pelvic irradiation. As with males, the degree of dysfunction is dependent upon the total dose received and the age at time of treatment (Table 2) [4,53,56,57]. The lethal dose required to kill 50% of the oocytes (LD_{50}) has been estimated to be less than 4 Gy [57]. Consequently, ovarian failure may occur following treatment for pelvic/inguinal disease. In a study of 2068 women, 91% of who were aged >40 years, ovarian failure was reported in 97% of patients when treated with 5–10.5 Gy [58]. Significantly, higher doses (20 Gy) are required to destroy the fixed pool of oocytes and induce ovarian failure in prepubertal females [56].

6.3.2.2. Chemotherapy. The ovary is less susceptible to the effects of cytotoxic chemotherapy than the testis although, as for males, the alkylating agents are the

Table 2
Radiotherapy-induced damage to the reproductive tract

Gender	Site	Effect
Males	Cranial/total body irradiation TBI/pelvic/testes	Endocrine axis disruption **Germinal epithelium** >1.2 Gy–azoospermia 0.1–1.1 Gy–oligoozospermia **Leydig cells** >20 Gy–pre-pubertal >30 Gy–post-pubertal
Females	Cranial/total body irradiation TBI/abdomen/pelvic	Endocrine axis disruption **Ovarian failure (LD_{50} < 4Gy)** older women >5 Gy younger women >20 Gy **Uterine damage** decreased volume decreased elasticity

LD_{50}, lethal dose to kill 50% of the oocytes; TBI, total body irradiation; Gy, Gray (unit of radiation).

most gonadotoxic Treatment with MVPP (mechlorethamine + vinblastine + procarbazine + prednisolone) or ChlVPP result in ovarian dysfunction in 38–57% of patients [4,53]. The incidence of overt ovarian failure increases with increasing age of the patient at the time of treatment. The larger number of surviving primordial follicles available after treatment may explain the apparent 'resistance' of the prepubertal ovary and relative protection afforded to younger females. The impact of chemotherapy on ovarian function and subsequent recovery is often unpredictable and may vary with time. Oligomenorrhoea occurs in some females, which may either progress to premature menopause or be followed months to years later by the return of normal menses. Interestingly, recovery of menses is also reported in a small number of females following a period of ovarian failure, although the underlying mechanism is unknown [59]. Long-term follow-up is essential because a successfully treated proportion of women may go on to develop a premature menopause [60]. It is likely, though not yet proven, that the hybrid regimen (three cycles of ABVD alternating with three cycles of ChlVPP or MOPP) will decrease the prevalence of ovarian dysfunction.

6.3.3. Females—uterus

Abdominal, pelvic and total body irradiation has been shown to result in reduced uterine volume and decreased elasticity of the uterine musculature, possibly as a consequence of impaired vascularisation [62]. Thus, radiation damage to the uterus may impair fertility and result in an increased prevalence of miscarriages [56]. In addition to the deleterious effects of cytotoxic chemotherapy and radiotherapy on the ovary, the damage to the uterus may impair its capacity to carry a successful pregnancy. Although successful pregnancies following radiotherapy are reported, the incidence of premature delivery and intra-uterine growth retardation is significantly increased [61–64].

6.3.4. Cardiotoxicity

6.3.4.1. Radiotherapy. Early and late cardiac effects are recognised following chemotherapy and radiotherapy treatment for Hodgkin's disease, and include cardiomyopathy, pericarditis, valvular lesions and coronary artery stenosis, though many of these reports concern treatment practices that are now considered out of date [65–69]. For instance, high dose (>40 Gy) mantle field radiotherapy has been associated with pericarditis in 30–40% of patients, abnormal ECG (electrocardiogram) abnormalities in 25–50% and abnormal left ventricular function in half of patients [66,67]. In a study of 2232 paediatric Hodgkin's patients, with mean follow-up of 9.5 years, and a total 21 164 person-years of follow-up, the risk of cardiac death in patients treated with mediastinal radiotherapy, with or without chemotherapy, relative to the general population was 3.1 (95% confidence interval (CI), 2.4–3.7)). Absolute risk of cardiac death was 28 per 10 000 person-years (males: 40.0 and females: 11.9). There was no increased risk among patients who did not receive mediastinal radiotherapy [65].

These days, radiotherapy techniques have been revised to include fractionation with lower total doses in combination with chemotherapy and insertion of subcarinal blocks with doses above 30–35 Gy to limit cardiac irradiation. This has brought about dramatic reductions in cardiac-related mortality. Limitation of cardiac exposure has led to a reduction in cardiovascular risk from 4.3 to 2.6, and reduction of absolute risk falling from 48.9 to 15.3 excess deaths per 10 000 person-years [41].

6.3.4.2. Chemotherapy. Anthracycline-induced cardiotoxicity is commonly reported and although a 'safe dose' has yet to be defined, the extent of damage increases with increasing drug exposure and time from treatment. There is little information on the frequency of anthracycline-induced cardiac toxicity following treatment for Hodgkin's disease. In a large study of 6493 children treated for cancer with anthracycline therapy, cardiotoxicity was confirmed in 106 (1.6%) of the patients [68]. Cardiotoxicity occurred within 1 year of completion of treatment in 90% of the 106 patients. Factors associated with an increased risk of anthracycline-associated cardiotoxicity included a high cumulative dose of anthracycline ($\geqslant$550 mg/m^2), female sex, black race, presence of trisomy 21 and concurrent treatment with amsacrine. In a study of 120 relapse-free acute lymphoblastic leukaemia (ALL) survivors treated with daunorubicin, 90–270 mg/m^2, 23% demonstrated reduced left ventricular shortening and 2% had reduced contractility [69]. The incidence of cardiac abnormalities is low with cumulative anthracycline doses less than 300 mg/m^2 [70].

The introduction of hybrid chemotherapy protocols, with a reduced total dose of anthracyclines, is likely to result in a decrease in cardiac toxicity. Schellong reported one case of (moderate) chronic cardiomyopathy in more than 1200 patients treated with a total doxorubicin dose of 160 mg/m^2 [26]. Follow-up of 57 patients treated with six cycles of the hybrid therapy MOPP/ABVD and involved field radiotherapy for 6.7 years, did not show any evidence of cardiac disease [20]. A low incidence of cardiac disease has also been reported by other groups using low dose anthracycline therapy [25,28,37,65]. The prevalence of late anthracycline cardiotoxicity is unknown, long-term follow-up therefore remains essential if the full treatment burden is to be determined.

6.3.5. Second malignancies

One of the most devastating consequences of aggressive cancer therapy is an increased risk of second primary malignancies. Exposure to radiation is associated

with a significant risk of developing solid tumours, particularly breast cancer, sarcomas and thyroid cancer [71–73]. Chemotherapy, particularly with the alkylating agents, is known to be associated with the development of leukaemia [74–76]. The development of leukaemia is maximal at 5 years post-treatment, while the incidence of solid tumours increases with time post-treatment [71–77].

The relative risk of developing any second malignancy, as reported at Stanford in a study of 694 children, was 15.4 for females (95% CI, 10.6–21.5) and 10.6 (95% CI, 6.6–16.0) for males followed up for a median of 13.1 years (1–31.6 years) [72]. The actuarial 20-year risk was 13.25%, 9.7% for males and 16.8% for females. Similar actuarial risks of 8.0 and 12.7%, at 15 and 20 years, respectively, have been reported by Green and colleagues [73] and confirmed by other groups [71,77].

6.3.5.1. Radiotherapy. Girls and young women who receive mantle irradiation of greater than 40 Gy have a significantly increased risk of developing breast cancer, with age at the time of treatment the strongest risk factor [41]. The Stanford experience of 885 women followed up for 10 years demonstrated a relative risk of 136 for girls treated before the age of 15 years, and a relative risk of 19.2 (95% CI: 10.3–32) for those women treated before age 25 years and a greatly increased relative risk of 136 (95% CI: 34–371) for those girls treated before age 15 years [78]. It is important to emphasise that the incidence of breast cancer is very strongly influenced by the dose of radiotherapy. The Stanford group has reported that since the introduction of combined modality therapy over the past 25 years, allowing a reduction in radiotherapy dose and volume, no cases of breast cancer have been observed [41].

Females are also reported to be at greater risk of non-breast second malignancies than males [71,79]. In a study of 499 patients with Hodgkin's disease, treatment with radiotherapy alone (25%), chemotherapy (6.0%) or both (69%), followed up for 9 years (range 0.1–27.4) second malignancies were significantly more common among female patients than males ($P = 0.002$), even when those with breast cancer were excluded ($P = 0.007$) [71]. An interesting, but predictable, observation from this study also noted that relapse is associated with a significantly increased risk of developing second primary cancers [71].

6.3.5.2. Chemotherapy. Over the last 20 years, it has become evident that the high incidence of second haematological malignancies (2–6% at 10 years) following treatment of childhood Hodgkin's disease is largely attributable to alkylating agents and topoisomerase II inhibitors [74–76,80]. These treatment-induced leukaemias commonly present as acute non-lymphoblastic leukaemias (ANLL) or myelodysplastic syndromes (MDS) and have a poor prognosis. Different chemotherapeutic agents are responsible for two distinct types of leukaemia. The alkylating agents, particularly mechlorethamine and cyclophosphamide, procarbazine and the nitrosoureas, predispose to a type of t-ANLL with a peak incidence 5 years post-Hodgkin's treatment. These leukaemias are frequently associated with chromosomal abnormalities, usually deletions, of chromosomes 5 and 7 [75]. However, topoisomerase II inhibitors, including the epipodophyllotoxin etoposide, anthracyclines and dactinomycin, are associated with the development of distinct forms of leukaemia, which generally present within 5 years following treatment for Hodgkin's disease [76]. Most of the chromosomal translocations involve disruption of a breakpoint cluster region of the Mixed Lineage Leukaemia (*MLL*) gene on chromosome band 11q23. High cumulative doses of topoisomerase II inhibitors are associated with the appearance of *MLL* translocations early in the course of treatment for Hodgkin's disease and may account for a 5–12% risk of developing leukaemia, particularly M4/M5 type acute myeloid leukaemia (AML), MDS, chronic myeloid leukaemia or ALL [80,81].

Regular physical examination, with careful attention to the skin, breasts and thyroid, may facilitate early detection of the most common second malignancies in long-term survivors. Self-breast examination and regular mammography from 5 years after treatment may be particularly important. The results of systematic long-term follow-up studies will give crucial information. Chemoprevention with Tamoxifen is effective in reducing the incidence of breast cancer in high-risk populations and its use in female childhood survivors is currently under consideration [82].

6.3.6. Pulmonary toxicity

Sequential pulmonary function tests have demonstrated parenchymal lung damage and fibrosis after radiotherapy and bleomycin chemotherapy, but with modification to treatment protocols the incidence of lung damage is substantially less than previously reported [20,25–27,83]. With the hybrid regimen MOPP/ABVD (total bleomycin dose: 60 U/m^2) and low dose radiotherapy (15 Gy), none of the 57 patients studied had symptomatic pulmonary disease, although mild abnormalities of lung function tests including restrictive and obstructive defects and reduced carbon monoxide diffusion capacity (DLCO), were reported in 32%. The long-term clinical consequences of these changes are not yet known [20].

7. Balancing the risks

These days most children and adolescents developing Hodgkin's disease have an excellent chance of cure at the expense of a number of treatment-related side-effects

in later life. Over the past 20–30 years, systematic attempts have been made to reduce these 'late effects'. Treatment with combined modality therapy, enabling fewer cycles of cytotoxic chemotherapy and reduced doses of radiotherapy, has been shown to sustain the high cure rates, while at the same time affording considerable reduction in long-term morbidity. Cardiac disease, thyroid disease and second malignancy, particularly breast cancer, have been substantially reduced following modifications to radiotherapy practice. Changes in chemotherapy practice, by eliminating or reducing the dose of mechlorethamine, may reduce the incidence of second haematological (t-ANLL) malignancies. Infertility is almost universal in males, with ovarian dysfunction and risk of premature menopause in 50% of females, following six courses of alkylating agent-based treatment. The introduction of the anthracycline-based regimen, ABVD, has significantly reduced the incidence of infertility, especially in men, but is offset by the potential development of cardiac disease.

7.1. Individualisation of treatment

Increased recognition of therapy-related side-effects and patient 'informed' involvement in the decision-making are assuming greater importance in the individualisation of treatment. For stage I disease, treatment with chemotherapy with or without radiotherapy, or radiotherapy alone have comparable efficacy, so the 'late effects' issue is of particular importance. In the UK, young patients and those with mixed cellularity histology (who respond less well to radiotherapy alone [21]) are treated with four courses of hybrid chemotherapy (ABVD/ChlVPP) as the impact of radiotherapy has greater cosmetic problems, particularly in the younger child. Older patients with stage I disease, excluding mixed cellularity, will be given the choice of hybrid chemotherapy or radiotherapy alone.

7.2. Does gender matter?

For patients with low stage disease, the cure rates are excellent regardless of the chosen regimen, yet the side-effects profile differs between males and females. Consequently, it may be pertinent to consider the gender of the child when determining the most appropriate treatment. The high prevalence of breast cancer in female survivors of childhood Hodgkin's disease is attributable to mediastinal radiotherapy. Elimination of radiotherapy and application of chemotherapy-only regimens has been successfully employed by a number of centres. The impact of late toxicity on male and female fertility also warrants separate consideration. In theory, the hybrid protocols enable a reduction in dose of any one agent and may reduce gonadotoxicity. However, infertility still occurs in some male patients treated with as few as three courses of MOPP (50%) [55]. Perhaps treatment with ABVD only regimens may be the most appropriate regimen for young boys. Female patients appear to be less sensitive to the gonadotoxic effects of chemotherapy and it is hoped that the reduced doses of alkylating agents in the hybrid chemotherapy regimen will not result in premature ovarian failure, although only long-term follow-up will confirm or refute this supposition. Females are also particularly vulnerable to sub-diaphragmatic irradiation and patients with early stage disease may be better treated with chemotherapy only. Regardless of the regimen administered it is important, where possible, to take appropriate steps to preserve fertility. Cryopreservation of sperm should be offered to all post-pubertal boys who are planned to receive alkylating-agent-based chemotherapy, and in some centres cortical ovarian strips are being collected from young females for potential use at a later date [84]. The harvesting of ovarian cortical strips for cryopreservation remains experimental and raises many ethical issues including consent, safety and future use of stored material [85,86]. Responsible practice in this area is a subject of continuing debate and many groups are working towards the development of a voluntary code of practice [87,88].

8. Conclusions

The major obstruction to determining the optimal treatment for young people with Hodgkin's disease are a lack of large multicentre randomised trials and the relatively long lag period between treatment and the emergence of late side-effects. The highest cure rates appear to be achieved using risk-adapted combined modality therapy using limited numbers of cytotoxic cycles and low dose involved field radiotherapy in high stage disease. Over the past decade, 'hybrid' chemotherapy protocols have been introduced in an attempt to reduce late sequelae. Hybrid chemotherapy protocols combine drugs with high efficacy in curing Hodgkin's disease, while at the same time reducing late toxicity. These modifications to chemotherapy regimens will limit the total exposure to alkylating agents, anthracyclines, procarbazine and bleomycin and are likely to decrease the prevalence of sterility, haematological malignancies and cardiopulmonary disease.

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