CHAPTER 21 COMPLICATIONS OF TREATMENT

21.1 Introduction

The use of radiotherapy and or chemotherapy can result in a wide range of acute and chronic side effects. These are generic concerns for cancer treatment in general. Side effects include bone marrow suppression, and cardiac and lung damage. A full discussion is beyond the scope of this document. These guidelines deal with complications that are of greater significance in younger patients with lymphoma, including infertility, secondary malignancy and psychosocial effects of treatment.

21.2 Infertility

There are no randomised studies comparing the incidence of infertility after various chemotherapy regimens for lymphoma. The data presented here are based on descriptive series and in some cases, personal communications from respected authorities.

21.2.1 After conventional-dose chemotherapy

Hodgkin lymphoma

Sperm counts may be low to start with in men with extensive disease prior to treatment.[1] Old-style regimens such as MOPP (or, to a lesser extent, MOPP-ABVD) commonly caused infertility.[2] However, the commonly used current regimen, ABVD, may cause temporary oligospermia or irregular menses for several months[3,4], but rarely, if ever, permanent infertility in either men or women (Joseph Connors: personal communication: no cases of infertility in 200 women treated with 2–6 cycles of ABVD). The effect on fertility of more aggressive regimens such as BEACOPP is not known, although any regimen containing procarbazine is likely to cause infertility in men. Pelvic irradiation is rarely administered for Hodgkin lymphoma (HL) in the modern era. If performed in young women, it is usually done with oophoropexy (surgical movement of the ovaries to the midline behind the uterus, or high up at the pelvic brim, away from the field of radiotherapy) and ovarian shielding. Men can have testicular shielding, which reduces the dose to below that which causes infertility.

Low-grade lymphoma

A variety of treatments including low-dose alkylating agents (e.g. chlorambucil, cyclophosphamide), fludarabine and monoclonal antibody therapy are commonly used. Alkylating agents can cause gonadal failure and infertility. The incidence depends on age, particularly in women (higher age = higher infertility) and the cumulative dose.[5] Azoospermia is universal at total chlorambucil doses above 400 mg, but sperm counts may recover in some patients after a period off chemotherapy.[6] Irreversible germinal aplasia following cyclophosphamide is uncommon until at least 6–10 g has been administered.[7] Conventional doses of cyclophosphamide, vincristine and prednisolone (CVP) are unlikely to cause permanent infertility.[8]

There is little data on the effect of fludarabine on fertility. One report on a 47-year-old man documented a significant reduction in sperm count during treatment.[9] There are no data on fludarabine in combination with other chemotherapy drugs. There is no reason to believe that naked antibody therapy with anti-CD20 monoclonals (rituximab) and anti-CD52 monoclonals (Campath-1H) should influence gonadal function, but no record of this been formally evaluated has been sighted. The impact of radio-labelled anti-CD20 antibodies such as iodine-131 tositumomab (Bexxar: Ashwin Kashyap: personal communication) and yttrium-90 ibritunomab tiaxetan (Zevalin) has also not been evaluated.

Intermediate-grade lymphoma

Surprisingly, there is little formal data in large numbers of patients of the fertility effects of conventional CHOP (6–8 courses at three week intervals), the most widely used regimen in this

context. CHOP is associated with temporary effects on fertility in both sexes (6–18 months of oligospermia is not unusual in men), which generally recovers thereafter (Joseph Connors: personal communication). Infertility is uncommon at conventional cumulative doses of cyclophosphamide (4.5–6 g/m^2) with CHOP-like chemotherapy and in the absence of pelvic radiotherapy.[10] The paucity of published data cannot exclude the possibility, however, that a small percentage of men may be persistently azoospermic and that women who recover ovarian function may be at risk of premature menopause.[11] The effects of more intensive approaches, including giving CHOP each two weeks instead of the traditional three weeks, or with the addition of VP16, is unknown (Michael Pfreundschuh: personal communication).

Other regimens used in the past, but less frequently today, include MACOP-B or VACOP-B. These have little impact on future fertility.[12] Hyper CVAD/araC-MTX is now being used for advanced mantle cell lymphoma, a disease predominantly of older males. No fertility studies have been done in this patient population (Jorge Romaguera; personal communication). An intensive regimen used by the French (LNH-80) involving 6 g/m^2 cyclophosphamide and multiple other chemotherapy agents resulted in infertility in only 15% of males evaluated after long-term follow up.[13]

High-grade lymphoma

Many of these are treated with acute leukaemia-based regimens. The limited published data suggest that any effect on fertility is likely to be temporary.[14] CODOX-M/IVAC is an aggressive regimen for Burkitt's lymphoma; anecdotally, men have regained fertility after this protocol (Ben Mead: personal communication).

General comments

In men who have received chemotherapy but recovered fertility, the quality of sperm is not affected.[15] Other studies have shown no evidence of a higher incidence of congenital anomalies in children born to men or women who have had prior chemotherapy.[16] A recent review evaluated pregnancy outcome among sexually active male survivors of childhood cancer, comparing the results with their brothers who had not had cancer.[17] The male:female ratio of the offspring of the two groups was 1.0:1.03 versus 1.24:1.0 respectively ($p = 0.016$), raising the possibility of a relative deficit of male infants among the offspring of the partners of male survivors. The proportion of pregnancies of partners of male cancer survivors that ended with a live-born infant was lower if the male had been treated with dactinomycin or procarbazine doses >5 mg/m^2. Other chemotherapy did not effect the rates of live birth and of stillbirth.

Key point

The implications of chemotherapy on fertility should be discussed with all patients for whom this is relevant.

Guidelines — Chemotherapy	Level of evidence	Refs
For patients receiving conventional chemotherapy for lymphoma (ABVD for Hodgkin lymphoma, CHOP q21 for lymphoma), sperm cryopreservation in men or oocyte retrieval (in women) is not recommended routinely.	IV	3, 4, 10

This advice should be individualised, however, in patients:

- requiring pelvic or testicular radiotherapy
- with poor-risk disease, who may need early intensified therapy and stem cell transplantation

- receiving newer regimens such as fludarabine-based protocols and CHOPq14 or CHOP-VP16. In these circumstances, the possibility of infertility should be discussed where relevant, and referral to an appropriate specialist considered.

The impact of delaying chemotherapy on the management of the disease needs to be taken into account.

21.2.2 After high-dose chemotherapy/transplantation

A number of factors influence the likelihood of recovering fertility and gonadal function after transplantation. These include gender, age, prior treatment, nature and intensity of conditioning, and possibly after allografting, the extent of chronic graft versus host disease (GVHD). Some general observations are as follows:

Recovery of fertility after high-dose cyclophosphamide alone, as used in conditioning for aplastic anaemia, usually occurs in men and women towards the end of the first year post-transplant, although recovery is age-dependent in women and such treatment may induce an earlier onset of menopause.[18]

- High-dose busulphan-cyclophosphamide causes permanent ovarian failure in the vast majority of women, but in men, over half will recover some degree of spermatogenesis.[19,20] The risk of azoospermia may correlate with the extent of chronic GVHD. Sperm counts tend to recover in the second year post-transplant and may progressively increase over the next three years.

- Recovery of fertility occurs in 10–20% of patients in adults after cyclophosphamide — total body irradiation (TBI) — although the incidence is dependent on age (especially in women) and TBI dose.[19] Recovery after TBI may take four to seven years. There are few data on high-dose alkylator combinations such as busulphan-melphalan. The incidence is not well documented after BEAM, but there are anecdotal reports of recovery of fertility in both sexes.[20] There are no published data after use of fludarabine-containing reduced-intensity conditioning regiments.

- In general, pregnancies after transplants usually have a successful outcome, although there appears to be a higher risk of complications such as preterm delivery and low birthweight babies in female recipients who receive TBI[21], possibly because of effects on the endometrium and myometrium.

21.2.3 Preservation or restoration of fertility after sterilising chemotherapy

Males

Pre-chemotherapy

(i) Prevention of gonadal damage: there are data suggesting that testosterone may reduce the risk of azoospermia from long-term treatment with cyclophosphamide.[22] Conversely, completely withdrawing testosterone from the testis using gonadotrophin releasing hormone (GnRH) agonists before (or even after) chemoradiotherapy protects and/or restores sperm counts in a rodent model.[23] Both these approaches are experimental and should only be used in the context of clinical trials.

(ii) Sperm retrieval: the usual practice is to offer semen cryopreservation prior to high-dose treatment, preferably after a period without any exposure to chemotherapy.[24] This can be collected by masturbation or by testicular biopsy if an ejaculated specimen is not possible pre-treatment. Semen cryopreservation should be offered to oligospermic patients as non-assisted fertilisation, for example, intracytoplasmic sperm injection (ICSI) means that very few sperm are necessary for successful fertilisation.[25] Experimental strategies include cryopreservation of testicular tissue or isolated germ cells (reviewed in Bone Marrow Transplant).[26]

Post-chemotherapy

(i) Fertility: men with low sperm counts post-treatment may be fertile; 30% with idiopathic infertility and sperm counts between 1–5x10^6/ml (normal >20x10^6/ml) may be expected to father children within two to three years. One approach in persistently azoospermic patients post-chemotherapy, if sperm collection has not been performed beforehand, is a testicular biopsy; occasionally sperm are present, which may then be collected, stored and subsequently used for ICSI.

(ii) Hypogonadism: after high-dose chemotherapy, roughly 10% of men, particularly those over 45–50 years, have low testosterone levels and symptoms of hypogonadism such as fatigue, poor muscle strength and low libido.[27] Recent reports suggest adrenal androgen deficiency may not be uncommon.[28] Erectile dysfunction is not uncommon and is often related to cavernosal arterial insufficiency as demonstrated by colour-flow Doppler.[28] Testosterone replacement and sildenafil may be effective.[29]

Females

Pre-chemotherapy

(i) Prevention of gonadal damage: There is no proven treatment that prevents infertility in women receiving high-dose chemotherapy. There is one report of the oral contraceptive pill protecting ovarian function in women receiving chemotherapy for Hodgkin's lymphoma. More recent research has focused on the use of GnRH agonists in this context.[26,30] These are being assessed in continuing clinical trials, as are GnRH antagonists (Kate Stern: personal communication). The theory is to suppress ovarian function through decreased secretion of pituitary gonadotrophins. While there are promising animal data, evidence suggesting that radio-chemotherapy directly destroys primordial follicles (which are not cycling) independent of gonadotrophin status raises doubts about the usefulness of these approaches in humans receiving sterilising chemotherapy.[11]

(ii) Oocyte retrieval[26]: options include:

- oocyte retrieval after superovulation, in vitro fertilisation and embryo cryopreservation pre-transplant, then subsequent embryo transfer of thawed embryos post-transplant when wishing to conceive[31]

  This is not possible in children. Implantation of a viable embryo currently is associated with a 15–20% chance of pregnancy.

- oocyte retrieval pre-transplant, cryopreservation, subsequent thawing and fertilisation by sperm followed by embryo transfer

  This is less successful than embryo cryopreservation, in part because of lower survival of oocytes after freezing and thawing. It may carry risks such as chromosomal loss and spindle anomalies.[11]

- ovary cryopreservation and either subsequent reimplantation of the intact ovarian tissue post-transplant *or* subsequent in vitro maturation of oocytes followed by fertilisation and embryo transfer

  Some centres offer freezing of small slices of ovarian tissue retrieved laparoscopically prior to transplant. One advantage of this procedure is that, unlike oocyte referral, it can be arranged at short notice without undue delay in initiating chemotherapy. It has not yet been proven in adult humans that fertility can be restored by these approaches, although preliminary studies are encouraging.[32,33] Tumour contamination is a concern. There are limited data regarding the incidence of overt or occult ovarian involvement by lymphoma. Involvement by HL is probably very rare[11], but old data suggest that involvement by non-Hodgkin lymphoma at autopsy (presumably in patients with disseminated lymphoma) is not infrequent.[34] Moreover, using a mouse lymphoma model, investigators have shown that transmission of lymphoma to graft

recipients can be mediated by cryopreserved ovarian tissue samples taken from donors with lymphoma.[35]

Post-chemotherapy

(i) Fertility: in the absence of patient oocytes, in vitro fertilisation using donated ova and partner sperm.[36]

(ii) Hypogonadism: in addition to symptoms such as hot flushes and vaginal dryness, oestrogen insufficiency may contribute to loss of bone mineral density, which frequently occurs post-transplant, particularly in the first six months.[37] Women of post-menopausal age usually require short- to medium-term hormone replacement therapy (HRT); younger women who may potentially recover fertility usually receive the oral contraceptive pill till age forty, and then HRT until age fifty, the average age of spontaneous menopause. HRT may have a beneficial effect on bone density.[38] Topically administered vaginal oestrogen cream is often used to provide adequate local oestrogenisation. Some patients have low testosterone levels and persistent problems with loss of energy and libido, despite adequate oral oestrogen replacement. They may benefit from androgen replacement therapy in the form of transdermal testosterone cream.[39]

21.2.4 Sexual activity and pregnancy early after chemotherapy

There are few data in the literature to assist in recommendations in this area. A murine study found cyclophosphamide in the seminal fluid of treated males, longer retention of cytotoxic in the seminal fluid than plasma, and an adverse effect on implantation.[40] There are no data to our knowledge of cytotoxic levels in vaginal secretions.

Chemotherapy-induced sex chromosomal and autosomal aneuploidy in human sperm declines to pre-treatment levels in 90 days.[41] Based on approximately three-months period for a complete cycle of spermatogenesis, the use of contraception where relevant is recommended for six months after chemotherapy, to limit the risk of transmitting these defects.

Key points

In patients receiving high-dose chemotherapy prior to transplantation, the following are recommended:

(a) *Pre-transplant*: referral to a fertility specialist. In women, the possibility of chemotherapy-induced premature menopause, and the acute and long-term effects of this, should be explained. Use of a continuous contraceptive pill during therapy is not unreasonable in pre-menopausal women, but is not proven. If available, enrolment in a trial evaluating GnRH agonists or antagonists should be considered.

(b) *Post-transplant*:

Women

(i) if ovarian failure occurs, HRT should be considered, if appropriate

(ii) regular surveillance of gonadal function off HRT to detect spontaneous recovery of fertility may be indicated in selected patients

(iii) regular gynaecological review (by a gynaecologist with particular interest and expertise in post-transplant issues such as oestrogen deficiency, infection, and, in allograft recipients, vaginal graft versus host disease, is strongly recommended), cervical cytology, and, in those receiving HRT, mammography

(iv) bone mineral density scans in women not on HRT, particularly if there are other risk factors for osteoporosis

(v) testosterone levels should be checked in patients with symptoms suggestive of androgen deficiency

Men

(i) regular surveillance of gonadal function post transplant

(ii) enquire about libido and erectile dysfunction. Consider

(a) testosterone replacement if low testosterone levels and symptomatic, and

(b) sildenafil if erectile dysfunction and no contra-indication.

Guidelines — Advice to patients	**Level of evidence**	**Refs**
During cytotoxic therapy, sexual intercourse can continue, but reliable contraception should be used. Condoms should used be used within 48 hours of chemotherapy if the male is treated, to avoid seminal transmission of cytotoxics, particularly if the female partner is pregnant.	IV	41
Sperm banking should be offered to males who are receiving potentially sterilising chemotherapy and who may wish to have children in the future.	IV	24, 25
Women receiving chemotherapy in which fertility and/or premature menopause are relevant should discuss the potential impact of their treatment on these issues with their oncologist and, in some cases, with a fertility expert.	IV	11, 31–33
Conception of a child by men (and possibly by women) should be delayed for at least three months until after the completion of cytotoxic therapy affecting the gonads.	IV	41

21.3 Secondary malignancy following treatment

21.3.1 Introduction

While advances in the treatment of HL and lymphoma have resulted in many long-term survivors, it is clear that survival does not come without risk.

Second malignancy is the leading cause of death in survivors of HL[42], and is considered to be the most serious consequence of therapy. Long-term follow up demonstrates an increased risk of myelodysplasia and leukaemia in chemotherapy-treated patients, and of solid tumours in those whose treatment included radiation.[43] The influence of chemotherapy in the occurrence of solid tumours is less clear.[44]

The risk of developing leukaemia and lymphoma has been demonstrated to be greater during the first decade following treatment, then reducing and reaching a plateau midway through the second decade.[45] In contrast, the risk of developing a solid tumour continues to increase with time. The highest risk is in those patients surviving longer than fifteen years. Solid tumours as a second malignancy have been documented out to twenty years and beyond following treatment.[45,46]

Assessment of the risk of second malignancies is confounded by the long latency, especially for solid tumours, and the relative rarity of such events. Most analyses are performed comparing incidence in large survivor databases with incidence in 'normal' populations to produce ratios of observed to expected (O/E) incidence. These analyses span a number of decades over which treatment practices may have altered significantly. Heterogeneity, both with regard to type of disease and treatment, should be considered when interpreting results.

The risk of second cancers appears to be higher in patients treated for HL[47] than in lymphoma and other malignancies (Table 21.1). This suggests that disease related factors might play a role in the development of secondary malignancy in HL.

Table 21.1 Risk of all second cancers by first primary diagnosis irrespective of treatment

First primary cancer	Relative risk
Hodgkin lymphoma	2–4
Non-Hodgkin's lymphoma	1.2–1.4
Chronic lymphocytic leukaemia	–1.3
Ovarian	1.2
Cervical	–1.4
Testicular	–5.0
Colorectal	1.0
Breast	1.3

Source: Holland, Blast & Morton[47]

21.3.2 Second haematological malignancies

After treatment for Hodgkin lymphoma

Acute non-lymphoblastic leukaemia (ANLL) accounts for most cases of secondary acute leukaemia. Observed rates of secondary leukaemia show significant acceleration in the risk of ANLL following treatment, but the absolute increase in risk is small and diminishes dramatically by ten years. Radiotherapy appears to play only a minor role in accelerating the risk of secondary leukaemia.[48] Regimens that contain mustine[49] and chlorambucil[50] have been associated with higher rates of ANLL than ABVD.[48] Newer regimens such as ABVD are associated with a lower risk of leukemia[48], with a fifteen-year actuarial risk of 0.7%, which is similar to the rates observed with radiation alone.[51] The use of escalated-dose BEACOPP has been associated with a potential increase in the five-year actuarial risk of secondary AML/MDS compared with COPP-ABVD (0.4% versus 2.5% p=0.03).[52]

In a large cohort of 1984 patients treated over a twenty-year period with a variety of regimens, including MOPP, ABVD and MOPP/ABV, the risk of lymphoma was increased[53], with a relative risk of 21.5. Some late cases occurring beyond ten years were noted.

After treatment for non Hodgkin's lymphoma

A review of >29,000[54] patients treated from 1973 to 1987 showed an overall increase in the risk of second cancers, with the O/E ratio reaching 1.77 at ten years. The risk of leukaemia following treatment for lymphoma of various histologic types has been shown to be increased[55]. Mustine derivatives have the greatest risk, and cyclophosphamide is associated with a non-statistically significant increase in leukaemia risk. In this cohort, radiotherapy did not increase the risk of leukaemia.

Another cohort study[56] examined >6000 subjects with lymphoma who survived two years after diagnosis. At two years, there was an increase in the risk of leukaemia, with an (O/E) ratio of 4.83. Among fifteen-year survivors there was an increased risk (O/E ratio 1.37) for second solid tumours (of all types), and a significantly increased risk of HL (O/E ratio of 25).

21.3.3 Second solid tumours

Radiotherapy

Radiotherapy has consistently been associated with an increase in the risk of solid tumours. The contribution of chemotherapy is more variable.[53] Relative risk ratios for solid malignancies are much lower than for leukaemia, but the absolute number of cases is higher, with solid tumours accounting for more than 50% of secondary malignancies in most reported studies, and up to 90% in one series.[53] Patients treated at a younger age appear to be at higher risk[53], with relative risks of all second cancers shown to be increased 14-fold in children treated before the age of ten[43],[43] particularly those treated with high-dose extended field radiotherapy.[43,57,58]

Breast and thyroid cancers are the most common solid second malignancies in the irradiated population, followed by bone and connective tissue, skin, GIT, and brain, tumors.[43,59] Elevated risk persists for more than twenty years, with an increase in risk for female breast, thyroid and bone at ten years, and elevated risks of cervical and digestive tract tumours becoming apparent in the second decade of follow up[43].[43]

Breast cancer

The influence of age at irradiation on risk is particularly evident in breast cancer, the most common second malignancy in female survivors of HL, who received mantle irradiation. Those aged less than fifteen at time of irradiation have the greatest risk; with an O/E ratio of up to 39 reported in women between the ages of ten and nineteen at the time of breast irradiation[43,60,61]. Women aged thirty or more at the time of irradiation had no increased relative risk[61].[61] Clinical and pathologic features consistently reported in studies of breast cancer occurring after treatment of HL includes: the median latency period between treatment and diagnosis of fifteen years, with 95% occurring after ten years following radiation; histopathologic characteristics similar to primary breast cancers; and medial and bilateral cancers observed more frequently than in the non-irradiated population.[60,62,63]

Thyroid cancer

An increased risk of thyroid cancer after exposure to radiation, either directly or from scatter irradiation, has been reported after irradiation for HL, lymphoma and several other paediatric tumours.[43,44,53,59,64,65] While the thyroid gland in children has been shown to be particularly sensitive to the carcinogenic effects of radiation, Japanese reports have also indicated an increased risk in irradiated adults[64].[64]

Thyroid cancers caused by radiation begin to appear five to ten years after exposure. The greatest relative risk occurs after fifteen to twenty years. However, increased risk has been shown to be present at fifty years, and is likely to persist for life[46].[46]

The most common type of radiation-induced thyroid cancer is papillary carcinoma. Tumour behaviour does not appear to differ from spontaneously occurring tumours at the equivalent age[46].[46]

The use of screening in these patients remains controversial. However, ultrasound has been shown to be a useful non-invasive tool in screening for thyroid abnormalities[66].[66]

The role of chemotherapy

Whilst the relationship of second solid tumours related to chemotherapy is less certain, the additive role of chemotherapy to radiation has been suggested in several studies. A specific review of secondary bladder cancer as a second malignancy[67] demonstrated a dose–response relationship with cyclophosphamide and bladder cancer (Table 21.2). Radiotherapy did not contribute to the increased risk of bladder cancer in this study

Table 21.2 Relative risk of bladder cancer with cyclophosphamide dose escalation

Dose of cyclophosphamide	Relative risk of bladder cancer
<20 g	2.4
20–49 g	6
>50 g	14.5

Conclusion

There is ample evidence demonstrating the risk of second cancers developing after treatment for HL and lymphoma. With long-term follow up, about 10% of patients develop a second malignancy. The most commonly seen haematological malignancy is ANLL, and the most common solid tumours are breast and thyroid cancer. Changing chemotherapy and radiation schedules may result in a change in the frequency of second malignancies with contemporary treatment. More intensive therapy, both chemotherapy and radiotherapy, may be associated with greater risk. Some agents appear to carry specific risk, for example, mustine. Patient variables such as age at diagnosis and gender, as well as disease variables, for example, HL, also influence the risk. The effects of current treatment protocols on the risk of secondary neoplasia are most common before ten years for subsequent haematological malignancies, whereas solid tumours may not become evident for more than ten years.

Guidelines — Advice to patients	Level of evidence	Refs
Patients should be informed about the risks of second malignancy at the time of treatment as well as at completion of therapy.	IV	42–46
Patients should be informed about the effects of smoking, diet, sun exposure and lifestyle habits that may increase their risk of developing second malignancy at specific sites, such as lung, skin, breast, digestive tract and cervix.	IV	55
Lifelong surveillance for secondary cancers is appropriate. A management plan should be organised for surveillance relevant to each individual patient, with the patient, their family and the general practitioner.	IV	42–46

Key points

- More intensive chemotherapy and radiotherapy may both be associated with a greater risk of second malignancy.
- All patients should have at least annual full blood examination for the first decade after treatment.
- In women younger than thirty treated with mantle radiation, routine annual mammography from seven to eight years after treatment is recommended in addition to regular self-examination and six-monthly physician examination. Abnormalities should be further investigated with ultrasound and biopsy.[49,53,68-70]
- The safety of hormone replacement therapy in postmenopausal women who have received mantle radiation is uncertain. There is some evidence that oestrogen deficiency may reduce risk of secondary breast cancer.[53, 68,70]
- The role of screening tests for second thyroid cancer for patients treated with radiation therapy to the head, neck and chest, is uncertain. Ultra-sound and physical examination can be used at appropriate intervals, for example, one year post-completion of therapy, then three-yearly to ten years, followed by annual thyroid ultrasound from ten years after treatment. Given the greater incidence of this complication following radiotherapy in childhood, it may be more important to screen this population.

21.4 Psychosocial effects of treatment of lymphoma

Quality of life in long-term survivors may be affected by physical acute and chronic medical complications from chemotherapy and radiotherapy. In addition, there is a range of potential psychosocial problems that may result from the impact of the diagnosis of a life-threatening illness, the rigours of treatment, and the attendant social disruption. There are few studies adequately addressing these issues. Most studies include patients with a variety of diagnoses, including solid tumours, and many only study the early period after treatment, and not long-term adjustment. Older studies may have less relevance due to improvements in management. Some comprehensive studies involving controls have been performed in patients with HL and childhood cancers, but none specifically study patients with lymphoma. Studies of the ability of survivors to obtain insurance and employment have been performed in the United States and Europe, but may not be directly comparable to the opportunities and standards currently existing in Australia.

21.4.1 Health-related quality of life

The quality of life of long-term survivors of lymphoma has not been well studied. Hospital-based studies of adults with HL compared with matched controls have found that energy levels had not returned to patients' satisfaction in 37% of cases[71].[71] Similarly, more physical impairment and chronic fatigue has been reported[72]. In addition, significantly greater restriction in performing strenuous activities and lower overall health for as long as ten to eighteen years after treatment has been observed[73].[73] Although not systematically studied, physical limitations that have an impact on global quality of life, such as fatigue and dyspnoea, may not be seen with the same frequency in patients with lymphoma, compared with HL, in whom sterility and early menopause has been more common and where gonadal failure may contribute to symptomatology. Health-related quality of life in patients at one-year post autologous stem cell transplantation was little different from those having combination chemotherapy for lymphoma[74].[74] A higher level of fatigue reported in the autografted group of patients has been postulated to relate to gonadal failure[75].[75] The impact on quality of life of

long-term treatment-related complications, such as osteoporosis, has not been studied, nor has the effect of CNS prophylaxis or treatment in adults with lymphoma.

21.4.2 Psychological complications

Early psychological effects

Anxiety and depression was assessed prospectively in patients with lymphoma and shown to be most prevalent at the time of diagnosis, but likely to recur[76].[76] There are no studies specifically addressing the immediate impact of treatment-related side-effects on psychological wellbeing and quality of life in lymphoma. This study[76] also concluded that alopecia, mucositis and change of taste contributed to psychiatric morbidity. There are no studies that address whether the severity of immediate side-effects of treatment has any effect on long-term psychological health.

Psychological distress and adaptation

A study comparing adolescent and adult patients with HL at a median of two years after treatment with controls found subtle, non-impairing psychological distress. Although most measures of psychological dysfunction did not differ significantly from controls, a significant number of patients reported increased irritability[77].[77] These authors report denial as a principal coping mechanism, but some patients had symptoms of a post-traumatic stress syndrome. Similar to these findings, a more recent study did not find an increase in late psychological distress in adult patients with HL compared to controls[72].[72] In contrast, one study found that long-term psychological adaptation does not occur to the same degree in adult survivors of HL[78], with psychological distress being elevated by one standard deviation above that of healthy subjects.

Two studies, although containing small numbers of adult patients with lymphoma, suggest that survivors are typically accepting and adapt to the changes in their lives.[79,80] These studies are the only reports of the frequency of mental health disturbance as a long-term complication in survivors of lymphoma.

One study, which assesses the psychologic and neuropsychologic function of patients after autologous bone marrow transplantation, showed that patients with haematological conditions including HL and lymphoma showed more distress than patients with breast cancer, but became less distressed over time[81].[81]

Depression

Depression correlated with symptoms of fatigue in survivors of HL in one study.[71] A large survey of survivors of paediatric lymphoma showed a significantly increased risk of reporting symptoms of depression, with intensive chemotherapy adding to the risk[82].[82] However, suicidal ideation in survivors of paediatric and adult HL does not appear to differ significantly from controls[77].[77] One study in adults, in which 50% of the patients had lymphoma, suggests an increase in depression and fear of relapse for an average of four months after diagnosis[**76**].[76] Although anxiety and depression was seen more at diagnosis, new episodes occurred throughout the year post-diagnosis, but patients were only followed for twelve months.

Memory and cognitive disturbance

Cognitive disturbance was reported in the majority of adult survivors, but only objectively found by neuropsychological testing in a subset in patients with both HL and lymphoma[80], and in a group with HL alone[72] compared to controls ($p = 0.15$). Survivors with lymphoma complained of memory disturbance (not confirmed by formal testing), which may be a reflection of increased anxiety and depression.[76,80] Verbal memory and psychomotor functioning was found to be significantly reduced in patients with breast cancer or lymphoma receiving systemic chemotherapy, compared with local therapy only[80].[80] Higher-order cognitive functioning generally worsened over time.

21.4.3 Social complications

Interpersonal relationships

A study comparing age- and sex-matched healthy controls found that adult survivors of HL had reduced social functioning (interference with family life and friendships; p = 0.048), with no statistical difference in emotional status[72].[72] There are no similar studies in lymphoma.

A large cohort of patients who had survived childhood cancer, including 85 patients with lymphoma, were studied[83].[83] When adjusted for effects of income, education, age at follow up and vital status with controls, there was no decrease in the incidence of marriage, live-in relationships or rate of divorce. In contrast, a study in HL patients[84] suggested a higher divorce rate for men than compared to the general population. The timing of divorce in relation to therapy was not reported.

Sexual function

In an uncontrolled study of patients with HL, over a third of patients complained of sexual problems[78].[78] Decreased sexual interest and activity and a feeling of reduced physical attractiveness has been reported in patients with HL, in whom infertility historically has been of greater incidence.[77,71] Most modern regimens are not sterilising and effects on sexual functioning are unlikely to be as significant. A 20% overall incidence of loss of libido at one year after diagnosis was seen in a study of 57 patients with lymphoma[**76**].[76]

Education, employment and social status

The psychosocial effects of childhood and adolescent HL, at least five years after completion of treatment, have been studied. Although subjects had missed a mean of six months of school and 40% reported unpleasant school experiences, their educational levels exceeded those of a matched population. There was no increase in alcohol or drug abuse[84].[84] In this study and another study of survivors of childhood HL[77], almost all subjects said that they had benefited in some way from the experience of having a malignancy. However, most expressed concerns about discrimination in employment and in obtaining life or health insurance.

In contrast, studies of adult survivors of HL suggest that they experience job discrimination and have lower employment rates than the general population, resulting in a negative socioeconomic effect from their diagnosis and treatment.[71,78,84] In addition, they have a low incidence of obtaining life insurance policies and have difficulty obtaining finance.[72,73] There are no studies addressing financial discrimination of patients surviving lymphoma. An early prospective English study of patients with lymphoma showed a high proportion of healthy patients who did not return to employment, with 18% not working for more than twelve months or retiring early[76].[76] Retirement was more frequent in females and older patients.

21.4.4 Summary

There is a paucity of prospective, systematic and contemporary studies evaluating the psychological impact of the diagnosis and treatment of lymphoma.[85,86] The limited data available suggest that clinicians should be mindful of the possibility of psychological disturbance in the short and long term and, with the assistance of a multidisciplinary team, support patients who are experiencing social, financial or employment difficulties. Most studies suggest depression and anxiety occur early, with most patients learning to adapt. Paediatric patients may be more vulnerable to late depression. Hypogonadism may contribute to psychological symptoms. Interpersonal difficulties may be most acute during treatment, but sexual difficulties may be related to hypogonadism, and self image related to infertility. Memory and cognitive disturbance may occur from treatment and could affect social interaction and work performance. Although there are no studies to evaluate its benefit, early intervention with the provision of counselling and support to both patient and partners would seem prudent. Continuing support, with assistance with work, family, and financial and life goals, may benefit those experiencing discrimination or suffering from uncertainty about their future health.

Patients may require intervention to cope with increased anxiety at the time of clinical reviews and dealing with fear of relapse. Anxiety and depression may require referral to appropriate health care professionals.[87]

Guidelines — Physician alerts after treatment for lymphoma	Level of evidence	Refs
Multidisciplinary care enhances psychosocial and sexual functioning, with fertility counselling and management of hypogonadism.	IV	76, 85, 86
Clinicians should be alert to symptoms of depression even in the longer term, particularly in the paediatric population.	III-2 IV	71, 82, 76, 82
Memory and cognitive disturbance may occur after systemic chemotherapy and may be worsened by anxiety, particularly at the time of clinic attendance. Patient interviews may need to be enhanced with written material and diagrams.	IV	72, 80
At the patient's request, clinicians may need to communicate with the education facility and/or workplace (with regard to patient privacy) to counter discrimination in employment or study.	IV	71, 77, 78, 84
Chronic fatigue and prolonged restriction of strenuous physical activity may follow treatment for lymphoma.	IV	71–73

21.5 Blood donor/organ donor

21.5.1 Blood donor

As lymphoma is a blood-borne disease, lymphoma patients should never donate blood.

21.5.2 Organ donor

For the same reason, lymphoma patients are never suitable as organ or tissue donors. The one exception appears to be corneas, although this should be at the discretion of the state licensing authority.

Key points

- Patients should understand that they should not donate blood or organs.
- Keep the patient's treatment team and other doctors informed.

21.6 References

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