Management of lymphoma in pregnancy

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Summary: One in every thousand pregnancies is complicated by a concurrent diagnosis of cancer. Lymphoma is currently the fourth most common malignancy diagnosed during pregnancy and its incidence is rising. The diagnosis and management of any malignancy during pregnancy is clearly a clinical and emotional minefield for both patients and health-care professionals. The major challenge is to optimize medical treatment offered to the mother, while limiting the impact on the fetus. Given the relative rarity of the situation, current practice is guided by case reports and personal experience of management of similar patients. Our centre has a large and busy lymphoma practice, and has cared for several women diagnosed with a variety of subtypes of lymphoma over the years. This review aims to summarize current opinion about best practice regarding these patients and discusses options available from the current literature.

Keywords: lymphoma, pregnancy

GENERAL OVERVIEW OF LYMPHOMA

Lymphoma is an umbrella term for a large heterogeneous group of malignancies (>30 subtypes) that are characterized by an uncontrolled proliferation of lymphocytes. Patients present with a variety of symptoms: with the development of palpable lymphadenopathy, or classic constitutional B symptoms of weight loss, fatigue and night sweats. There has long been debate as to the best way to classify these diseases into more homogenous disease entities with similar behaviour and prognoses.¹ The World Health Organization modification of the REAL classification recognizes three major categories of lymphoid malignancies based on morphology and cell lineage: B-cell neoplasms, T-cell/natural killer-cell neoplasms and Hodgkin's lymphoma. Both lymphomas and lymphoid leukaemias are included in this classification because both solid and circulating phases are present in many lymphoid neoplasms and distinction between them is artificial (Figure 1).

Patient characteristics and incidence

Hodgkin's disease is a relatively uncommon malignancy, with an annual incidence of 2.33/100,000. In women, the incidence peaks in the third decade and then falls, whereas in men the incidence remains relatively stable from the third decade onwards. In comparison, the incidence of non-Hodgkin's lymphoma (NHL) has risen dramatically since the mid-1950s and is currently 17/100,000. This rise is partially attributable to the observed rise in HIV-associated lymphomas. Although it can be diagnosed from the second decade onwards, the incidence rises significantly with age.

Treatment

Lymphomas have been treated in the past with a variety of combinations of multi-agent chemotherapy and radiotherapy.^{2,3} Radiotherapy to areas of localized disease can be given either as the sole treatment modality in early-stage disease, or as an adjunct to chemotherapy in high-risk lymphomas for those with evidence of residual disease after the completion of chemotherapy.⁴

The last few years have seen an explosion in interest in molecularly targeted therapies against lymphoma cells. The most widely used agent is Rituximab, a murine-human chimeric monoclonal antibody specific against CD20, an antigen commonly expressed on the surface of B lineage malignancies.⁵ Because of its specific nature in targeting B-cells alone, its side-effect profile is substantially lower than with other chemotherapy regimens.

Prognosis

As one would expect from such a heterogeneous group of disorders, the prognosis varies widely dependent on a number of factors. These include age and initial performance status, as well as tumour specifics such as histological subtype, grade and stage. Such factors often influence the type and intensity of treatment offered to patients, as well as being a useful tool for patient stratification within clinical trials.^{6,7}

Hodgkin's disease is unique among lymphomas in being exquisitely chemotherapy sensitive. In the last 15 years, response rates to treatments have increased to such an extent that is viewed as one of the most curable of all malignancies. The prognosis of NHL is more variable. In very general terms, high-grade, aggressive lymphomas (those with a high proliferation rate), such as diffuse large B-cell lymphoma (DLBCL) or Burkitt's, require urgent treatment, but have a high likelihood of cure if they respond to initial rounds of

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Figure 1 World Health Organisation (WHO) simplified classification system of lymphoma

chemotherapy. Low-grade lymphomas follow a more indolent path and do not necessarily require immediate treatment at diagnosis, but achieving long-term cure in the context of widespread disease is extremely unlikely.⁸

LYMPHOMA IN PREGNANCY

Current figures suggest that about one in 6000 pregnancies is complicated by a new diagnosis of lymphoma. Epidemiological studies suggest that this is a similar incidence to an age-matched non-pregnant cohort of women. Histological analysis suggests that the frequency of subtype, stage and prognosis of those with Hodgkin's disease is the same in both pregnant and non-pregnant cohorts. However, the same principle does not hold for other types of lymphoma: NHL diagnosed during pregnancy tends to represent the more aggressive end of the disease spectrum, with an increased incidence of high-grade subtypes such as Burkitt's.⁹ The reason for this difference is not clear.

It is a widely held belief that lymphoma diagnosed in pregnancy is often widespread at the point of diagnosis. This may in part be due to the characteristics of the tumour itself (more aggressive subtype), the physiology of pregnancy (increased blood supply and hyperdynamic circulation) or particularly due to delay in diagnosis, with patients and doctors more likely to attribute unusual symptoms to pregnancy rather than other causes. Lymphomas diagnosed during pregnancy often present in unusual sites such as breast tissue and ovaries.

Investigation

It is important to stage all patients as fully as possible at diagnosis as this often dictates the need for treatment and type of treatment. Formal tissue biopsy (normal lymph nodal tissue) can often be achieved with local anaesthesia only, but the biopsying of deeper structures may require a general anaesthetic. General anaesthesia is accepted as relatively safe during pregnancy and should not be a contraindication to obtaining a

diagnosis. Bone marrow aspirates and trephines (normally obtained from the external iliac crest) are similarly safe.

Standard work up involves full body computerized tomography (CT) or CT-positron emission scanning (PET) staging¹⁰ to gauge extent of disease before therapy. However, both techniques involve a substantial abdominal irradiation dose, which is contraindicated during pregnancy. It is not yet clear as to whether the ¹⁸F-FDG isotope used for PET scanning is safe in pregnancy, but it is known to permeate across the placenta. To limit the fetal radiation dose, many centres are performing chest imaging with either chest X-ray or CT, with sub-diaphragmatic lead shielding. The abdomen can be partially staged by the use of abdominal ultrasound scanning. Alternatively, magnetic resonance imaging (MRI) is widely believed to be safe in pregnancy and is a sensitive alternative to full body CT scans.¹¹

Learning point: MRI, where available, is the imaging of choice in pregnant patients. Ultrasound scanning is also a safe and useful adjunct

MANAGEMENT

Even the largest lymphoma practice will have limited experience in dealing with pregnant patients. Management should encompass a multidisciplinary approach involving coordination between oncology, haematology and obstetrics staff, ideally in a centre with some experience of the problems. Any decision regarding management must be made with full discussion and informed consent of the patient, and there will often be a strong element of patient choice.

Learning point: Management of pregnant patients with lymphoma should involve the coordinated efforts of a multidisciplinary team of obstetricians, oncologists, haematologists and midwives.

DO YOU HAVE TO TREAT THE PREGNANT PATIENT?

The decision to treat is based on a combination of tumour grade, the stage of the pregnancy and patient preference. The treatment decision requires a balance of the fetal and maternal risks posed by the disease and its therapy on a case-by-case basis.

Treatment of lymphoma diagnosed in the first few weeks of pregnancy is more problematic than one that presents in the third trimester. For the later group of patients, in most cases treatment can be delayed until after delivery. After induced delivery, high dose chemotherapy and/or radiotherapy can begin as per normal practice.

Decisions are more difficult in the earlier stages of pregnancy. Some of the more indolent (but incurable) lymphomas do not require immediate treatment. If the patient is well and asymptomatic, a period of watchful waiting can be undertaken. Treatment can possibly be delayed until after delivery or breast feeding. For higher grade tumours, such a delay may compromise maternal chances of cure or survival. Decisions around treatment involve careful weighing up of the potential risks to both mother and fetus, and taking steps to limit fetal harm from therapy. For those with the most aggressive lymphoma subtypes (such as Burkitt's), most centres would advocate early therapeutic abortion before commencing treatment in all but the latest stages of pregnancy where urgent delivery should be undertaken to allow treatment to the mother. Therefore, the factors (Table 1) influencing

Table 1 Factors influencing the decision to treat

Aggressiveness of lymphoma
Stage of lymphoma
Natural history of lymphoma progression
Maternal co-morbidities
Gestational age
Side-effects of treatment
Invasive investigations required

the decision to treat are complex and need to be weighed up on a case-by-case basis.

CHEMOTHERAPY AND THE PREGNANT PATIENT

Most chemotherapeutic agents are of small molecular size and can easily permeate the placental barrier, thus potentially exerting harmful effects on the developing fetus.

Retrospective analysis, case reports and results from animal studies suggest that the risk of teratogenesis from chemotherapy is very dependent on the age of the fetus at the time of exposure. The risk is highest during the period of organogenesis (between the ages of 2 and 8 weeks), with an estimated 10–20% risk of major organ malformation during this period. Exposure after 16 weeks is associated with a much lower risk of severe malformations, or mental retardation. The administration of chemotherapy at any stage in pregnancy is associated with an increased risk of intrauterine death, fetal growth restriction (FGR), preterm delivery and low birth weight.

Not all chemotherapeutic agents are equally teratogenic. The antimetabolites, which act at the level of nucleic acid synthesis, are associated with a higher risk of poor fetal outcome than other agents. High dose methotrexate (commonly used in the treatment of highly aggressive DLBCL and Burkitt's lymphoma) is associated with a high risk of fetal malformation in the first trimester, and can cause fetal myelosuppression when used in the second and third trimester. Other drugs seem comparatively safe: there are no case reports of fetal toxicity from the use of vinblastine, one of the vinca alkaloid family, in the second trimester onwards.

It is logical to assume that the use of single agent regimes is less harmful than combination of drugs administered together. This is problematic, as all the regimens given with curative intent involve the concurrent administration of at least four agents. Some centres have been using single agent chemotherapeutic regimes (such as vinblastine or steroids) to gain a degree of disease control while limiting potential toxicity. Despite all of the above concerns, there have been several published retrospective series of standard multiagent chemotherapeutic regimens administered in a variety of stages of pregnancy, which suggest a more favourable toxicity profile than first predicted. These are discussed in more detail below.

CHEMOTHERAPY FOR HODGKIN'S LYMPHOMA IN PREGNANCY

Treatment for Hodgkin's disease normally involves between two and six cycles of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy. A retrospective case series following 19 patients treated with ABVD at all three stages in

pregnancy reported no congenital or psychological abnormalities with the offspring of the patients.¹² A smaller case series reported the progress of six patients, four of whom received ABVD and two of whom were treated with MOPP (an alternative regimen of mustargen, vincristine, procarbazine and prednisolone). Five of the patients were treated in the second trimester, and carried healthy pregnancies to term. The sixth patient was treated with MOPP in the first trimester of pregnancy and developed fetal hydrocephalus.¹³

CHEMOTHERAPY FOR NHL IN PREGNANCY

Low-grade NHL

Current treatment for low-grade lymphoma may simply involve a watch and wait policy provided the patient is asymptomatic and there is no evidence of any end organ toxicity or compromise. When the patient does require treatment, combination chemotherapy regimens such as cyclophosphamide, vincristine and prednisolone (CVP) are used. We have recently used CVP from the second trimester onwards in a woman with low-grade NHL. There were no obvious adverse effects on her baby.

Intermediate to high-grade NHL

Modern treatment of DLBCL, and other intermediate grade NHLs, normally involves the administration of between four and six cycles of cyclophosphamide, vincristine, prednisolone and adriamycin (CHOP) chemotherapy. There are several case series documenting good maternal and fetal outcomes for those exposed to CHOP in the second and third trimesters.^{14,15} There are a few isolated case reports documenting normal pregnancies in patients exposed in the first trimester.^{12,15} It is reasonable to extrapolate the data from CHOP and assume the toxicity associated with CVP in the later stages of pregnancy is limited.

The treatment of high-grade lymphomas (Burkitt's, DLBCL and those with CNS involvement at diagnosis) involves the use of intensive, myelosuppressive regimens, which often contain high-dose methotrexate. As discussed above, first trimester exposure is associated with a high risk of fetal malformations. In this context, patients are often advised to have a therapeutic abortion before beginning treatment. Interestingly, case reports do exist of patients in the second and third trimesters, successfully treated and cured, with normal fetal outcomes.¹⁶ Table 2 summarizes the current knowledge.

THE SHIFTING PARADIGM OF LYMPHOMA TREATMENT: IS IMMUNOTHERAPY SAFE IN PREGNANCY?

An area of exploding interest in haemato-oncology is immunotherapy – the use of targeted biological agents, which appears to offer efficacy combined with a very limited side-effect profile because of its specificity of action. The best known agent in current practice is Rituximab, a humanized monoclonal antibody against CD20, a B-cell marker. However, as an IgG antibody, it can cross the placenta and has the potential to affect the fetal B-cell population, as well as the healthy maternal cells.

Table 2 Relative safety of chemotherapy in pregnancy

Chemotherapy regimen	First trimester	Second trimester	Third trimester	References
ABVD	With caution	Relatively safe	Relatively safe	12,13
CVP	With extreme caution	Relatively safe	Relatively safe	14,15
CHOP	With extreme caution	Relatively safe	Relatively safe	14,15
High-dose methotrexate regimes	Not safe	Not safe	Not safe	16

ABVD = adriamycin, bleomycin, vinblastine and dacarbazine; CVP = cyclophosphamide, vincristine and prednisolone; CHOP = cyclophosphamide, vincristine, prednisolone and adriamycin

Rituximab has been used in pregnancy: both in malignancy and also for the treatment of pregnant patients with uncontrolled autoimmune disease. The available data are encouraging – one case report recorded a transient loss of fetal B-cells associated with in utero exposure.¹⁷ No other case reports of adverse fetal outcomes have been reported.^{18,19}

There are many other new immunotherapies in clinical practice and trials. Alemtuzumab is targeted against CD52²⁰ and Epratuzumab recognizes CD22. Modified versions of antibodies, attached to radioisotopes (i.e. ¹³¹I labelled Tositumomab, which binds to CD20)^{21–23} have been trialled with some effect in the relapsed low-grade lymphoma. It is probable that in the future, treatment of both haematological and solid organ malignancy will become increasingly reliant on such targeted therapy.

SUPPORTIVE MANAGEMENT

Chemotherapy does not just involve exposure to anticancer medication. All patients who receive combination chemotherapy for lymphoma will generally require substantial exposure to antiemetics after each cycle, with the most effective agents being the newer five HT antagonists, such as ondansetron. Safety data now exist for the use of these agents and other standard antiemetics in other situations in pregnancy (such as hyperemesis gravidarum).

A common reason for re-admission to hospital postmyelosuppressive chemotherapy is for treatment of neutropaenic sepsis, which is most likely to occur between seven and 10 days after the start of each cycle. Such infections must be treated vigorously with broad-spectrum antibiotics to prevent rapid onset of septic shock. Standard treatment consists of a combination of a broad-spectrum cephalosporin and an aminoglycoside (i.e. tazosin and gentamycin). The use of penicillins is widely believed to be safe in pregnancy, as is the use of gentamycin.

RADIATION THERAPY DURING PREGNANCY

Exposure of pregnant women, at all stages of pregnancy, to large doses of radiation therapy is associated with a significant risk of fetal harm. Cohort studies, such as those women who were pregnant when they were exposed to the post-Chernobyl fallout, have shown in particular that their offspring have a significantly higher risk of developing leukaemias and solid tumours in the first decade of life. However, the expected radiation effects, such as mental retardation and organ malformations, probably only arise above a threshold dose of 0.1–0.2 Gy.

This threshold dose is not generally reached with curative radiotherapy during pregnancy, provided that tumours are located sufficiently far from the fetus and that precautions have been taken to shield the fetus against leakage radiation

and collimator scatter. A large amount of data exist to suggest that carefully planned and considered radiation therapy to specific anatomical sites can be safe in pregnancy, and is certainly worthy of consideration.^{24,25}

The most common presentation for limited stage Hodgkin's disease is with cervical lymphadenopathy. Many centres have advocated treating such patients with single modality, localized radiation alone. During such treatment, heavy lead screening of the abdomen is required, to limit the radiation dose administered to the fetus. A number of case series report the safety of this technique: the MD Anderson Centre published a series of six patients successfully treated for Hodgkin's disease with supra-diaphragmatic radiation, all of whom went on to carry successful pregnancies to term.²⁶ Clearly the utility of this technique is limited to the treatment of disease above the diaphragm and there are attendant risks to the fetus via a direct effect or via scatter irradiation, which may not declare themselves till years later. Because of the inherent risks outlined above, asymptomatic or minimally symptomatic patients can be followed through the entire pregnancy without treatment, which is reserved for symptomatic or life-threatening disease.

Another approach taken by some centres is to avoid radiotherapy altogether during pregnancy and either control localized disease if required by a short dose of safe attenuated chemotherapy such as single agent vinblastine and treat with full dose chemotherapy postdelivery. Over a 21-year period, 17 pregnant patients with Hodgkin's lymphoma at the BC Cancer Agency have been treated with this approach. Eleven out of 17 patients did not require treatment through to term and six required vinblastine to control disease. Out of the 17, 13 are alive and well and two have died from Hodgkin's lymphoma, one from retroperitoneal sarcoma and one from acute myeloid leukaemia. All of the patients delivered normal children with an age range now of 2–21 years with no evidence of impairment.²⁷

OBSTETRIC ISSUES

Patients with lymphoma should be managed not just by oncologists, but also closely followed by a high-risk pregnancy team. Exposure of the fetus at any stage in pregnancy to chemotherapy is associated with an increased risk of FGR, and we would recommend close fetal monitoring as per standard protocols to ensure development is proceeding normally.

For a patient who has been treated with chemotherapy in the third trimester, it is important to plan delivery around rounds of chemotherapy, both for the safety of the mother and the child. Clearly, delivery should be avoided during a period of pancytopenia, which occurs between seven and 10 days after the administration of drugs, due to a high risk of sepsis and poor wound healing. Regimes for low- and intermediate-grade

lymphomas are rarely associated with thrombocytopaenia of a degree to cause excessive intra- or post-partum haemorrhage.

The data do not suggest any contraindications to patients attempting vaginal delivery. Indeed, if chemotherapy has recently been administered, or further cycles planned, avoidance of caesarean section is advisable due to problems with wound breakdown post-chemotherapy. Some of the indolent lymphomas can be associated with massive inguinal and pelvic lymphadenopathy, but there are no documented cases of this being a significant enough issue to cause difficulties with vaginal delivery.

BREAST FEEDING

There are few safety data regarding the excretion of chemotherapy agents into breast milk. Generally, we advise mothers undergoing active chemotherapy against breast feeding their children. Subsequent rounds of chemotherapy might be delayed to allow a brief period of initial feeding.

LONG-TERM OUTLOOK

Several retrospective case series have documented the long-term outcomes of the offspring of patients treated for a variety of malignancies during pregnancy. Most of these were reassuring, with minimal observed long-term morbidity in children exposed *in utero* to chemotherapy. The largest series followed 84 children born to mothers treated for a range of haematological malignancies. Of this group, 26 were treated for Hodgkin's and 29 for NHLs: all their children had normal physical, mental and psychological development documented during the 19-year follow-up period.¹²

FERTILITY AND SUBSEQUENT PREGNANCIES

Referral to fertility services, when possible, before commencing chemotherapy is strongly advised for all women of childbearing age who plan to have future pregnancies.

Exposure to chemotherapy is often associated with transient and reversible amenorrhea. However, some patients will go on to develop primary ovarian failure, which is particularly noted with exposure to alkylating agents (such as cyclophosphamide). Given that egg collection takes a matter of weeks to arrange, delaying chemotherapy is clearly not possible in those patients who present with life-threatening symptoms. It is also not possible in a patient who is pregnant at the point of diagnosis.

Chemotherapy will reduce a woman's fertility, but, equally well, there are cases of many successful and healthy pregnancies in women previously exposed even to intensive and prolonged regimens. Interestingly, there are no data that subsequent pregnancies increase the risk of lymphoma recurrence. One retrospective study of young women treated for both Hodgkin's and NHL during pregnancy followed their fertility for three years post-treatment. During that time, 31 became pregnant, 34 suffered primary ovarian failure and 19 women were classed as having 'relative' fertility (i.e. they had not yet become pregnant, but were having normal periods and luteinizing hormone/follicle-stimulating hormone levels were normal). Age over 30 at the time of treatment, high-dose treatments and lymphoma relapse were all associated with higher risk of primary ovarian failure.²⁸

Learning point: If time allows, offering referral to fertility services for all women of childbearing age prior to commencing chemotherapy should be mandatory.

HOW DO WE IMPROVE OUR MANAGEMENT IN THE FUTURE?

The management of lymphoma in pregnancy is a rare problem, and even the largest centres have limited individual experience. The current data are limited and largely consist of a series of case reports or retrospective series amassed from single centre experience. In their excellent recent review of the available literature, Pereg *et al.*²⁹ found only 400 articles of relevance, most of which were single case reports.

Single case reports and series are a valuable resource – but there is an obvious bias to publishing reports of trials of newer drugs, or unexpected side-effects, but with less interest in the larger cohort of patients who are treated successfully throughout pregnancy. We strongly recommend the instigation of an International Registry of Patients diagnosed with lymphoma during pregnancy, with the aim of collating individual centres' experience of these patients, to be used as a resource.

Learning point: There is a need for an international database collating information regarding patient and fetal outcome in those treated for all malignancies in pregnancy, to guide future recommendations.

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(Accepted 12 February 2009)