Challenging Problems: Coincident Pregnancy, HIV Infection, and Older Age

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With the application of modern chemotherapy and radiation techniques, most patients with Hodgkin lymphoma can be cured, regardless of initial extent of disease. However, the lymphoma sometimes presents coincident with certain other major conditions, including pregnancy, infection with human immunodeficiency virus (HIV) or older age, which complicate treatment and make management considerably more challenging. Specially crafted approaches to staging and treatment, including the addition of specific supportive care measures, are required in these situations. Pregnant patients with coincident Hodgkin lymphoma should be staged without the use of imaging requiring radiation and treated with an approach that includes initial treatment deferral when appropriate, single agent vinblastine and reservation of multi-agent chemotherapy for the small minority with very aggressive lymphoma. Patients with Hodgkin lymphoma and HIV infection can be given standard anti-lymphoma treatment but require intensive supportive care with highly active antiretroviral treatment (HAART) and prophylactic antifungal and anti-Pneumocystis antibiotics plus neutrophil growth factors. Standard staging and full dose multi-agent chemotherapy are necessary if older patients with Hodgkin lymphoma are to be afforded the best chance of cure but the final choice of the individual elements of treatment must respect co-morbid conditions and age- or other disease-related organ compromise. If appropriately chosen, these special measures permit delivery of safe, effective treatment and frequent cure of the Hodgkin lymphoma despite complicating pregnancy, HIV infection or older age.

Hodgkin Lymphoma during Pregnancy

Between 0.5% and 1.0% of cases of Hodgkin lymphoma present coincident with pregnancy, presenting the problem of optimally managing the lymphoma while giving the developing fetus the best chance of reaching term fully intact. Essentially two patients need to be managed, one with lymphoma and the other without but affected by the toxicity of any treatments chosen. Fortunately, when Hodgkin lymphoma is discovered during pregnancy it is almost always possible to control the lymphoma and allow the pregnancy to go to full term. The treating hematologist/oncologist, an obstetrician experienced in the management of high-risk pregnancy and a pediatrician/neonatologist familiar with hematologic problems in the neonate should work together as a team to plan overall management. Information about the best approach to management of coincident Hodgkin lymphoma and pregnancy is limited. What little we know must be drawn from several small series and anecdotal descriptions[1-9] addressing this issue; however, if complemented by careful clinical judgment and knowledge of the usual natural history of Hodgkin lymphoma, these limited experiences can provide useful guidance.

When Hodgkin lymphoma is discovered during pregnancy, standard staging tests, avoiding as much as possible the use of imaging that requires radiation, should be completed (**Table 1**). A single postero-anterior radiograph of the chest, with proper shielding, should be obtained to characterize the extent of mediastinal and pulmonary disease. Abdominal ultrasonography can identify the extent and size of retroperitoneal nodal disease with sufficient detail for proper management. Magnetic resonance imaging can

Table 1. Tests required for staging of Hodgkin lymphoma discovered during pregnancy.

1. Complete history searching for B symptoms or other symptomatic problems suggesting more advanced disease
2. Physical examination for lymphadenopathy or organomegaly
3. Complete blood cell counts
4. Serum creatinine, alkaline phosphatase, lactate dehydrogenase, bilirubin and protein electrophoresis (including albumin level)
5. Chest radiograph, PA view only, with appropriate shielding
6. Abdominal ultrasound for retroperitoneal lymphadenopathy
7. Certain tests are only required for specific Hodgkin lymphoma presentations

Test	Presentation/condition
Bone marrow biopsy and aspiration	B symptoms or WBC < 4.0 x 10^9/L or Hgb < 120 g/L (women), 130 g/L (men) or platelets < 125 x 10^9/L
ENT examination	Stage IA or IIA disease with upper cervical lymph node involvement (supra-hyoid)

also be used and is, at least theoretically, free of potential toxicity to the fetus; however, the amount of detail provided in excess of what can be found with ultrasonography is unnecessary and the safety of the intensive magnetic fields required is not fully established. The principle to be remembered when doing these tests is that it is not necessary to completely catalogue all disease but rather to search for sites that seriously threaten the immediate well-being of mother or child.

The majority of patients found to have Hodgkin lymphoma during pregnancy require no immediate intervention. As a general rule any treatment, radiation or chemotherapy, should be avoided during the first trimester unless severely threatening symptoms are present. Asymptomatic or minimally symptomatic patients can be followed through the entire pregnancy without treatment, which can be reserved for development of symptomatic or threatening disease. More than 50% of patients can continue the pregnancy to term without any treatment for the lymphoma. If symptomatic or threatening disease develops some authorities have recommended irradiation with special shielding.[1,5,8-11] However, use of therapeutic radiation during pregnancy may have deleterious effects on the fetus due to direct or scatter irradiation, which may not be evident until many years later. Because radiation unnecessarily endangers the fetus a better choice is systemic chemotherapy.

Some experience with the common multidrug regimens used for the treatment of advanced stage Hodgkin lymphoma has been reported.[1-6] MOPP (mechlorethamine, vincristine, prednisone and procarbazine) appears to increase the risk of spontaneous abortion and fetal malformations, especially if administered during the first or second trimester of pregnancy.[3] Based on these observations and the known carcinogenicity of alklyating agents such as mechlorethamine, cyclophosphamide, procarbazine and chlorambucil this class of agents should be avoided. On the other hand, ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) has been used during pregnancy, and the limited experience that has been reported has not identified obvious negative effects on the fetus, although the number of patients is still quite small and whether the trimester of exposure is important is unclear.

Rather than expose the fetus to the potential adverse effects of multiple agents, an alternative approach using single-agent chemotherapy should be considered. Vinblastine was first described for this use more than 40 years ago[12-14] and is a particularly attractive agent because of its high level of effectiveness against Hodgkin lymphoma in treatment-naïve patients (> 75% response rate) and modest acute toxicity. Although reported to be teratogenic in mice, no similar effect is apparent in humans at doses therapeutic for lymphoma, nor is the drug carcinogenic. The combination of a high level of effectiveness, minimal acute toxicity and low likelihood of a negative effect on the fetus make vinblastine a useful agent to suppress Hodgkin lymphoma during pregnancy. Infrequent doses at intervals of several weeks or longer can be given to keep the Hodgkin lymphoma under control until delivery at term, minimizing risks to mother and child. Progression despite vinblastine, which occurs quite infrequently, should be treated with full-dose ABVD because such evidence of chemotherapy resistance signals aggressive disease requiring multi-agent chemotherapy. Standard dosing of 6 mg/m^2 is quite unlikely to cause significant myelosuppression, but careful timing to avoid a blood cell count nadir near delivery is prudent. Patients who have been able to complete the pregnancy without treatment for the lymphoma can be fully staged and treated appropriately after delivery. Patients who require vinblastine can no longer be accurately staged and therefore should be treated with a full course of 6 to 8 cycles of multiagent chemotherapy.

We have managed 17 pregnant patients with coincident Hodgkin lymphoma at the BC Cancer Agency over the past 21 years using the approach described above. Eleven remained off treatment through term delivery and 6 required vinblastine to control disease. Of the 17, 13 are alive and well and 4 have died, 2 from Hodgkin lymphoma and 1 each from acute myeloid leukemia and a retroperitoneal sarcoma. All 17 delivered normal children who now range in age from 2 to 21 years (median 15). Although these children have not been systematically assessed, no overt abnormality has become apparent. Management built around conservative use of single-agent vinblastine has allowed normal term delivery of the children and effective management of the mother's Hodgkin lymphoma with a minimum of psychological stress and appears to be a reasonable approach to this rare problem of coincident pregnancy and Hodgkin lymphoma.

Hodgkin Lymphoma and Infection with Human Immunodeficiency Virus

The incidence of Hodgkin lymphoma in patients with human immunodeficiency virus (HIV) infection is increased as much as 5- to 10-fold above expected rates.[15-18] This increased incidence cannot be explained by more intensive surveillance or diagnostic errors. In addition, HIV-associated Hodgkin lymphoma is much more likely to be widespread at presentation and it pursues a more aggressive natural history. It is almost always associated with Epstein-Barr virus[18-21] and is much more likely to be of mixed cellularity or lymphocyte depleted histology.[15-18,20] Presentation in extranodal sites is common and even more noteworthy is the frequency with which HIV-associated Hodgkin lymphoma involves unusual extranodal sites or spreads to extranodal sites without first involving the spleen, a phenomenon almost never seen in classical Hodgkin lymphoma.[15-18,20,22-25] The bone marrow is much more frequently involved with an attendant negative impact on treatment

tolerance and prognosis.[18,21,25] More than 80% of patients present with advanced stage and the incidence of multiple extranodal sites is much higher than with classical Hodgkin lymphoma.[15,16,18,20,22-25] In addition, most patients present with B symptoms. Weight loss is common and may be multifactorial.[15,16,18,20,22-25]

The treatment of Hodgkin lymphoma coincident with HIV infection is challenging because of the frequency of opportunistic infections, likelihood of coincident organ dysfunction due to HIV or other viral infections such as hepatitis, and necessity to employ an array of anti-HIV, anti-infectious agent and supportive medications, all of which may interact unfavorably with the chemotherapeutic agents necessary to treat the lymphoma. The most successful approach to treatment combines vigorous supportive care consisting of antiviral and antifungal agents and neutrophil-stimulating growth factors with highly active antiretroviral agents (HAART) together with standard multiagent chemotherapy. With appropriate supportive care, regimens such as ABVD;[21,22,26,27] EBVP (epirubicin, bleomycin, vinblastine and prednisone);[24] BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and procarbazine);[28] MOPP/ABV hybrid;[22,29] and Stanford V[30] can be delivered. Greater than normal toxicity is typical but with judicious supportive care and coincident administration of HAART, patients can be given these modern multiagent programs. No comparative studies have been completed, leaving clinicians without firm guidance to choose among these regimens.[31] Disappointingly, even with intensive supportive care and proper chemotherapy, response rates and cure rates are lower than in the non-HIV-infected population. Most investigators have found median survivals of 1 to 2 years; however, the most recent series have documented considerable improvement in outcome in the era of vigorous HAART suppression of the HIV, meticulous supportive care and full-dose ABVD chemotherapy achieving 5-year overall survivals in excess of 60% to 70% in selected patients.[27]

The major innovation in treating HIV-associated Hodgkin lymphoma in recent times has been the widespread use of HAART before and during management of the lymphoma. Many studies have now demonstrated that the prognosis of such patients has dramatically improved since the wide adoption of HAART.[15,22,27,29,32-35] Much progress still needs to be made, however. Even in the most recent era, when HAART has lowered the incidence of coincident infectious complications of the HIV infection and suppresses the retrovirus itself, cure rates for Hodgkin lymphoma remain much lower than those achieved in patients without HIV infection.

Hodgkin Lymphoma in the Older Patient

Studies of prognostic factors in Hodgkin lymphoma show that older patients have a worse outcome.[36-47] Based on the 3052 patients we have seen with Hodgkin lymphoma in the province of British Columbia since 1960, approximately 15% of patients are over 60 years of age at the time of diagnosis and 7% are over 70. Patients younger than 60 years of age have an overall 5-year survival rate that exceeds 80%, while it is less than 50% for those older than 60.[45,46,48-53] This difference may be due to inherently more aggressive lymphoma in the older patient, but other reasons include less favorable distribution of histologic subtypes, more advanced stage at diagnosis, interference with treatment delivery due to co-morbid illnesses, delay in diagnosis, incomplete staging, inadequate adherence to treatment protocols and failure to maintain dose intensity. Of the factors that negatively impact prognosis in the older patient with Hodgkin lymphoma, one that is at least partially under the control of the treating oncologist is treatment intensity. In some, but not all, reported series examined for adequacy of treatment delivery, those who had similar doses to younger patients had equivalent outcomes,[41,45] whereas those who had dose reductions had a worse outcome.[39,41,45]

Strategies to improve the outcome for older patients with Hodgkin lymphoma can be divided into two general types: (1) Insistence that diagnostic and staging tests should be of uniformly high quality regardless of age; (2) Alteration in treatment technique. The first is widely applicable and available to every clinician seeing such patients. Diagnosis should rest on an adequate biopsy, preferably of an entire involved lymph node, reviewed by an experienced hematopathologist. Needle biopsies should be avoided. Staging should include the same tests as are standard for younger patients. With the omission of staging laparotomy and lymphangiography and routine use of modern generation CT scanners, older patients can be evaluated just as thoroughly as those who are younger.

Attempts to strengthen or otherwise improve the treatment for older patients have focused on either trying to deliver full doses despite reduced organ tolerance, usually requiring use of granulocyte-stimulating factors and other vigorous supportive care, or the use of special regimens designed specifically for the older patient. The use of MOPP-type, ABVD or MOPP/ABVD hybrids for older patients as been associated with a 5-year overall survival of approximately 50%,[37] and it is not clear that liberal use of growth factors and other supportive care measures has improved on this outcome.[48,49,51-55] Innovative regimens such as ODBEP (vincristine, doxorubicin, bleomycin, etoposide and prednisone),[52] CVP/CEP (chlorambucil, vinblastine, procarbazine, cyclophosphamide, etoposide and prednisone),[56] VBM (vinblastine, bleomycin and methotrexate)[57] and VEPEMB (vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone and bleomycin)[58] have not produced unequivocally better outcomes (**Table 2**). Only one randomized trial targeting older patients with

Table 2. Representative series of older patients treated for Hodgkin lymphoma.

Regimen	COPP-ABVD or BEACOPP	COPP	CHOP-21	BEACOPP	VEPEMB	ODBEP
Number	372	52	29	42	105	38
Median age, y	65	—	—	68	71	72
% with major co-morbidity	—	—	55	—	37	—
Stage – limited, %	34	16	38	0	46	0
Stage – advanced, %	66	84	62	100	54	100
Febrile neutropenia, %	15	6	31	—	10	14
Compete response, %	86	—	93	76	76	—
Median follow-up, mos	—	60	41	80	—	—
Progression-free survival, %	60 (5-y)	—	76 (3-y)	46 (5-y)	56 (5-y)	49 (5-y)
Overall survival, %	65 (5-y)	48 (5-y)	79 (3-y)	50 (5-y)	64 (5-y)	42 (5-y)
Fatal toxicity, %	6	—	—	21	2	—
Reference	50	49	63	59	58	52

Table 3. Overall treatment plan for older patients with Hodgkin lymphoma.

Stage group	Ann Arbor Stage with Cotswold modification	Treatment
Limited	IA, IIA, low bulk (< 10 cm)	ABVD × 2 + IFRT
Advanced	Any stage with B symptoms or bulky tumor (≥ 10 cm) or stage III or IV	ABVD until 2 cycles past CR (minimum 6)

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; IFRT, involved field radiotherapy; CR, complete response.

Hodgkin lymphoma has been reported,[59] comparing baseline-dose BEACOPP with alternating COPP/ABVD. BEACOPP did not improve on the results achieved with standard chemotherapy but did cause an unacceptable level of lethal toxicity, 21%.

How then should older patients with Hodgkin lymphoma be treated? A reasonable plan, based on stage and modified in consideration of co-existing organ dysfunction, can be based on the same principles that have proven so effective for younger patients (**Table 3**). For patients with limited-stage disease (stage IA or IIA, low bulk [< 10 cm]) optimal combination of brief chemotherapy and IFRT capitalizes on the virtues of each modality while minimizing its toxicity. We now know, based on results in patients of all ages, that in such a program only 2 cycles of ABVD are needed if followed by IFRT[60] and that IFRT is at least as effective[60,61] and, in older patients, definitely less toxic compared with extended field radiation.[62] Thus, older patients with limited stage Hodgkin lymphoma can be treated safely and effectively with 2 cycles of ABVD followed by IFRT. Among 36 such consecutive patients treated over the past 8 years at the British Columbia Cancer Agency we have had no deaths due to Hodgkin lymphoma and only 1 relapse. Additionally, we have not seen any lethal pulmonary toxicity, a particular concern when using bleomycin.

An optimal treatment approach for older patients with advanced-stage Hodgkin lymphoma has not been defined. A reasonable choice is to use standard ABVD, with its well understood spectrum of toxicity and known efficacy, supported by neutrophil growth factors if necessary to enable safe delivery of full doses. Attempts to improve on ABVD with novel regimens have not produced convincing evidence of superiority (**Table 2**).[52,55-59,63] Although it is necessary to eliminate bleomycin when treating patients who have pre-existing pulmonary disease or who develop any sign of respiratory compromise during treatment, there is no satisfactory substitute for it. Whether bleomycin is essential has never been examined in clinical trials but circumstantial evidence indicates that it may be possible to eliminate it with only modest or no impact on outcome.[64] This question is now being addressed in prospective clinical trials. For patients who have pre-existing cardiac dysfunction or have a significant decline in ejection fraction during treatment there is no well-defined alternative agent. At our center we have used etoposide as a substitute for the doxorubicin in ABVD for such patients without obvious reduction in efficacy; however, this has not been rigorously tested. For now, whether removing the bleomycin or substituting etoposide for doxorubicin compromises treatment outcome remains unknown but may be necessary to control toxicity. Finally, some older patients, especially those with quite advanced age, are simply too frail to tolerate standard chemotherapy. In such patients it is prudent to forego attempts to cure the disease and to employ single-agent chemotherapy and involved field radiation palliatively to control symptoms and maintain the patients' quality of life.

Ultimately, improvements in the treatment of Hodgkin lymphoma in older patients will await identification of

novel agents that can be added to or substituted into the basic ABVD regimen without increasing toxicity. Clinical trials in this patient population should emphasize novel agents that minimize hematologic, pulmonary and cardiac toxicity. A renewed interest in studying this special population is evident in several recent initiatives.[59,62,63,65] Such efforts should help improve the outcome for these patients and bring their survival up to the high levels that have been reached in younger patients.

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Conflict-of-interest disclosure: The author declares no competing financial interests.
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