How Is Hodgkin Lymphoma in Pregnancy Best Treated?

ASH Evidence-based Review 2008

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A 26-year-old woman who is 22 weeks into her first pregnancy presents with a new diagnosis of Hodgkin lymphoma (HL). In preparing for her treatment you wonder about the safety and efficacy of chemotherapy during pregnancy.

A comprehensive literature review was conducted to evaluate the safety and effectiveness of chemotherapy for pregnant patients with HL. Medline (1950 through April 14, 2008) and American Society of Hematology abstracts (2004–2008) were searched using the MESH terms "Hodgkin Lymphoma/Therapy" (4528 hits) AND "Pregnancy" (611825 hits). Seventy-three articles were identified, with 56 published in English (to which subsequent review was limited). After excluding papers on fertility rates and survival outcomes, 10 original articles and 3 reviews were retrieved and scanned for additional references. A second search using the MESH terms "Hodgkin Lymphoma" (27621) AND "Pregnancy" (611825) AND "Drug Therapy" (404381 hits) identified 54 additional articles. Nine were non-overlapping original publications pertinent to chemotherapy for pregnant patients with HL.

In total, 8 case reports, 9 case series and 2 case-controlled studies were identified that reported on the pregnancy and survival outcomes of pregnant patients with HL.

The case reports highlight specific outcomes for individual patients and their pregnancies following treatment with single-agent or combination chemotherapy for HL.[1-4,6,14,15] In one case report, a 38-year-old women diagnosed in the second trimester with stage IIIB HL was treated with weekly vinblastine followed by oral cyclophosphamide (CFA), which resulted in partial remission of HL and the delivery of a healthy boy at term but eventual progression of HL.[1] Other articles cite the use of single-agent vinblastine in the first trimester with no adverse effect on fetal development and favorable disease response and a single case of fetal syndactyly in a child born to a patient with HL who was treated with CFA alone during all three trimesters. Procarbazine and chlorambucil used early in gestation were associated with normal fetal development.[2,3] In a case reporting multiagent therapy, a 26-year-old patient with bulky mediastinal HL was successfully treated at 24 weeks gestation with 3 cycles of MOPP (mechlorethamine, vincristine, procarbazine, prednisone).[4]

The case series provide summary data. Ebert et al describe 24 cases of HL during pregnancy and report 2 cases of spontaneous abortion and 5 cases of fetal malformation following first trimester exposure to MOPP, MOP or cyclophosphamide plus radiotherapy. The remaining 15 mothers received ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine; n = 10), MOPP (n = 4), COPP (cyclophospamide, vincristine, prednisone, procarbazine; n = 1) in the first trimester (n = 5) or later. All delivered normal infants that remained healthy.[5] Multiagent therapy using COPP,[6] MOPP,[7] or MPP with vinblastine[8] in second and third trimesters was associated with favorable outcomes for pregnant patients and infants. One series examined the outcomes of 9 newly diagnosed and 8 relapsed pregnant HL patients (Stages IA-IIA: 16, Stage IIIA: 1); 7 were treated with supradiaphragmatic radiation during 10 to 30 weeks of gestation, 2 underwent therapeutic abortion, and 6 deferred therapy until after delivery. Two patients conceived while receiving chemotherapy (vinblastine and procarbazine). Six out of 9 newly diagnosed patients achieved lasting complete remission and 2 recurred following radiation therapy.[9] All patients treated with radiation delivered healthy newborns. A baby born to 1 patient who conceived while on chemotherapy died due to prematurity. Two case series, the first of 15 patients[10] and the second of 17 patients,[11] investigated cases of concomitant pregnancy and HL. Of the 32 patients, 13 chose therapeutic abortion. Eleven patients in stage I or II received supradiaphragmatic radiation; 10 achieved complete remission without evident fetal injury. Patients with advanced disease received vinblastine (n = 2), chlorambucil (n = 1) or multiagent chemotherapy (n = 2). Two of these patients later died of progressive disease. Standard ABVD, investigated in two case series, caused no adverse fetal outcomes in 13 patients in the first, second or third trimester.[12,13] One patient who opted to have dacarbazine omitted developed progression of HL 1 year later. The safety and efficacy of

the ABVD regimen has also been reported in pregnant patients with concomitant HIV and HL with excellent outcomes for the patient and the fetus.[14,15] Long-term clinical, neurological, cytogenetic and immuno-hematologic follow-up was reported to be normal in 26 children exposed to ABVD or MOPP in utero (all trimesters included)[16] and 12 out of 14 mothers who had been treated for HL while pregnant were reported to be alive and lymphoma-free.[17]

Two case-control comparative studies were identified. Survival of 21 pregnant patients with HL treated with MOPP chemotherapy, radiotherapy or a combination (often delayed/interrupted and completed after delivery) was similar at 5 and 12 years compared to 155 contemporaneous age- and stage-matched non-pregnant controls.[18] Long-term outcomes of 48 pregnant females with HL compared with outcomes of non-pregnant matched women of similar stage of disease, age, and year of treatment demonstrated similar 20-year survival.[19]

Evidence to support a chemotherapy recommendation for pregnant patients with HL is scant. Based upon a comprehensive literature review we conclude that ABVD is a regimen of choice (Grade 1C recommendation) if multiagent chemotherapy is to be used. ABVD appears to be a safe for fetal development when used in any trimester; however, even in aggregate, the reported cases are few and moderate levels of delayed toxicity in the child may well have been missed. Use of alkylating agents, especially in the first trimester, may be associated with fetal demise or teratogenicity and should be avoided. Continued efforts to collect data on all HL patients who elect to continue coincident pregnancy and long-term follow up of these patients and their children will be of great value to make broad recommendations. We suggest the establishment of a central registry of children born to HL patients to capture the long-term follow up.

Disclosures

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