To the editor:

Pregnancies after high-dose chemotherapy and autologous stem cell transplantation in aggressive lymphomas

Increasing numbers of young women are being cured by chemotherapy for aggressive non-Hodgkin lymphoma (NHL), and the possibility of fertility preservation after these treatments has received much attention. The most important risk factors for the development of ovarian failure are the woman's age at the time of first treatment and the number of cycles with alkylating agents.[1] High-dose chemotherapy with autologous stem cell transplantation (ASCT) is now an accepted curative therapy for young patients with high-risk NHL.[2] Very few reported pregnancies have been published after such intensive regimens, mainly because they were performed after relapse in heavily pretreated women.[3] To determine the role of the cumulative cyclophosphamide dose given sequentially or in a single dose with ASCT, we decided to analyze the pregnancy rate for all young women prospectively treated according to the lymphome non-Hodgkinieu (LNH) 87-2 protocol for aggressive NHL. This protocol included 1043 patients at 35 participating centers. Inclusion criteria and clinical results have been published.[4] Briefly, patients with newly diagnosed NHL were given chemotherapy ACVB (doxorubicin, cyclophosphamide, vinblastine, and bleomycin), 4 cycles and responding patients were randomized to receive sequential chemotherapeutic (CT) consolidation or a consolidative CBV regimen (cyclophosphamide 6 g/m^2, BCNU [carmustine] 300 mg/m^2 and VP16 [etoposide] 1000 mg/m^2) followed by ASCT. The total dose of cyclophosphamide (the main toxic drug for ovarian failure) was 10 800 mg/m^2 at the end of the procedure for the patients undergoing high-dose therapy and 7800 mg/m^2 for those given the sequential CT. Radiation therapy was not included in the protocol. Only women under 41 years of age at diagnosis were considered for the pregnancy rate evaluation. Among the 210 young women (median age at diagnosis: 27 years; range, 15-40 years), 109 were randomized for the consolidation: 56 had received the intensive arm and 53 the sequential chemotherapy. No hormonal treatment was mandatory, and no specific recommendation was given for further pregnancy. Fourteen women included in this prospective protocol had conceived at the last follow-up evaluation (December 1999). They had all received the planned treatment (intensive or sequential), and only 1 patient relapsed, received further treatment, and died; the remaining 13 women are alive in complete remission. See Table 1 for details.

We found that a small number of normal pregnancies can be achieved in women treated with chemotherapy for NHL whether or not high-dose therapy with ASCT is included. The pregnancy rate did not seem to have been impaired in the group treated with high-dose chemotherapy despite a total cyclophosphamide dose of 10 800 mg/m^2. On the other hand, these pregnancies occurred in the youngest patients and no pregnancy was observed in women over 29 years at NHL diagnosis in this group. The influence of age on ovarian function recovery after ASCT has already been published,[5] and some rare pregnancies have been published in recipients of allogeneic transplantation including total body irradiation (TBI).[6] In conclusion, the youngest patients at diagnosis of NHL can hope to recover normal fertility after first-line therapy even when high-dose chemotherapy is given; no birth defects have been observed, but a follow-up of the children is warranted. For the remaining women who wish to become pregnant after treatment, alternative chemotherapeutic regimens with lower doses of alkylating agents or other agents should be prescribed until oocyte or ovarian cryopreservation become routinely available.[7]

Table 1. Pregnancies according to the randomized consolidation arm

Parameter	Sequential CT (n = 53)	High-dose CBV (n = 56)
Women pregnant	5	9
Mean age, y (range)	28 (23-33)	23 (17-29)
Mean interval, mo*	52	65
Children	4	11
Abortion	1	0
Death in utero	0	1

Entries are numbers of patients unless otherwise indicated.

*Mean number of months between diagnosis and delivery; range for both groups, 24-108 months.

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