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LETTER TO THE EDITOR

Second hematologic malignancies after ABVD: Two case reports and a retrospective study of 183 Hodgkin lymphoma patients

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To the Editor

Secondary treatment-related cancers are a major problem in Hodgkin lymphoma (HL) survivors. Although solid organ tumours are most common numerically and have the highest absolute risk, acute leukaemia has the highest relative risk of all second malignancies, probably because of the relatively short latency and its rarity in the general population, and is almost always fatal. This can be linked to the use of MOPP chemotherapy (nitrogen mustard, vincristine, procarbazine and prednisolone). Since the 1980s, MOPP-only chemotherapy has been gradually replaced by ABVD, which contains less alkylating agents, and several groups suggest that this has led to a correspondingly lower risk of developing acute leukemia. Nonetheless, there are only a few reports worldwide on the incidence of hematologic malignancies following ABVD [1,4,9], and none from East Asia. In this report, we aim to determine the relative risks and time free of hematologic malignancies in a cohort of 183 patients with Hodgkin lymphoma treated uniformly with ABVD, with or without radiotherapy, and to perform a brief literature review on the topic.

We analyzed 183 Singaporean residents with Hodgkin's lymphoma treated at the National Cancer Centre from July 1990 to October 2008. We excluded 15 patients who received only truncated ABVD or who defaulted on treatment. The remaining 168 patients with Clinical Stage I to IV Hodgkin's lymphoma received between three to eight cycles of ABVD, with or without radiotherapy. Among them, 96 (57%) patients received radiotherapy, which included subtotal nodal radiotherapy in one patient, and involved field radiotherapy in the remaining patients.

With a median follow up of 66 months, two patients developed second hematologic malignancies: one Acute Myeloid Leukemia (AML), and one Diffuse Large B Cell Lymphoma (DLBCL), at 21 months and 107 months following ABVD respectively. Thus, the relative risk (RR) of developing AML and DLBCL are 87-fold (95% CI 12–616) and 58-fold (95% CI 8–415) compared to the general population in Singapore, respectively [11].

The patient who developed AML is a 56-year-old female who first presented in July 2006 with Ann Arbor Stage IIIA lymphocyte predominant Hodgkin lymphoma. She attained complete remission of disease following six cycles of ABVD. Twenty-one months later, she presented with a persistent cough and fever. Within three days of admission, she developed an exponential rise in leucocytes, peaking at 97×10^9 with 35% blasts. Flow cytometry of peripheral blood revealed elevated myeloid markers, in particular CD 13 and MPO. A PET scan done showed mild FDG avid nodes in the neck, mediastinum, axilla, abdomen and pelvis. Excision biopsy of one of the submental nodes revealed an infiltrate of blasts from AML. The bone marrow aspirate picture was consistent with AML of the FAB M1 type. Cytogenetic and molecular studies stratified the disease as poor risk. She was then started on etoposide and cytarabine, with idarubicin substituted with etoposide in view of previous adriamycin exposure from ABVD. Failing both induction and salvage chemotherapy, she underwent allogenic bone marrow transplantation. Despite successful engraftment, she relapsed and subsequently died from a suspected intracranial hemorrhage in July 2009.

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Table I. Summary of various studies determining relative risks/standardised incidence ratios (SIR) of AML and NHL after chemotherapy for Hodgkin lymphoma

Study	No. of patients	Chemotherapy	No. of AMLs	RR or SIR (AML)	No. of NHLs	RR or SIR (NHL)
Canada/United States (Boivin et al.) [1]	10 472	Mixed, including ABVD and MOPP	122	23.9 (1.5 for ABVD)	35	5.6
International Agency for Research on Cancer (Kaldor et al.) [2]	9 552	Mixed	163	9.0	–	–
British National Lymphoma Investigation (Swerdlow et al.) [3]	5 519	Mixed	45	14.6	50	14.0
German Hodgkin Study Group (Josting et al.) [4]	5 411	Mixed, including ABVD, COPP, BEACOPP	36	–	–	–
Netherlands (van Leeuwen et al.) [5]	1 939	Mixed	31	34.7	–	–
Stanford (Tucker et al.) [6]	1 507	Mixed	28	66.0	–	–
Oslo (Abrahamsen et al.) [7]	1 152	Mixed	9	24.3	8	–
Munich (Munker et al.) [8]	1 120	Mixed	8	20.5	22	25.9
Gustave Roussy (Dietrich et al.) [9]	892	Mixed, including ABVD and MOPP	8	27.6	8	50
Boston (Mauch et al.) [10]	794	Mixed	8	66.2	10	18.4

The patient who developed DLBCL is a 73-year-old female with Ann Arbor stage IIA Hodgkin lymphoma in October 1998. She also attained complete remission following six cycles of ABVD. About 107 months after ABVD, she presented with low back pain and lower limb weakness. MRI of the spine showed cord compression due to a mass lesion in T11 and patchy marrow replacement from metastasis involving multiple thoracic levels. She underwent posterior decompression and tumour excision. The histological diagnosis was diffuse large B cell lymphoma (DLBCL). Following a complicated post-operative course and in view of her poor performance status, she received palliative radiotherapy to the T6-L1 spine for local control.

A review of literature revealed that most reports include patients who had received a variety of chemotherapeutic regimes; few have included a subset analysis of patients who received only ABVD with or without radiotherapy (Table 1). A study by the German Hodgkin Study Group [4] had 304 of 5 411 Hodgkin lymphoma patients, treated with ABVD. After a median follow-up time of 55 months, one case of AML was reported, with an absolute risk of 8.61 per 10^5 person-years. No breakdown of the number of non-Hodgkin lymphomas (NHLs) observed post ABVD was provided. In another study at the Institut Gustave Roussy by Dietrich et al. [9], 60 of 892 patients Hodgkin lymphoma received ABVD. After a median follow-up time of 93 months, eight AMLs (RR 27.6) and eight NHLs (RR 50) were observed in 892 patients receiving a variety of chemotherapy agents, including ABVD and MOPP. No subset analysis for the ABVD group was available.

Boivin et al. [1] studied a pooled cohort of 10 472 patients from 14 cancer centers in the United States and Canada. After an average follow-up of 7.1 years per subject, they observed 122 leukemias (RR 23.9) and 35 NHLs (RR 5.6). Of interest, the RR of leukemia after treatment with ABVD was 1.5 (95% CI = 0.7–3.4), although the number of leukemias or NHLs developing in those who received ABVD was not provided.

These two cases illustrate the need to be vigilant for second hematologic malignancies during long-term follow-up after ABVD, especially so since both cases presented with advanced disease. To date, the duration of effect and how certain agents, in particular ABVD, contribute to these long-term risks remain poorly understood. We have considered only ABVD exclusively in our adult population, to help further define these risks. One potential criticism to our study is the relatively short median follow-up period of 66.35 months, which may not be sufficiently long to observe some hematologic malignancies. Also, given the relatively small numbers from this single center study, our results serve a more descriptive rather than statistically significant purpose at this point of writing. Given the poor prognosis of these second malignancies, more quantitative information on the effect primary treatment agents have on second cancer risks, and subsequent improvements in combination regimes, would help to prevent these ultimately fatal complications.

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