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LETTERS AND CORRESPONDENCE

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B-Cell Bradycardia: Carotid Sinus Massage by a High-Grade Lymphoma

To the Editor: A 75-year-old woman was admitted to the hospital with complaints of lightheadedness and diaphoresis. For the past two weeks, these symptoms would occur and resolve spontaneously and last from 10 to 60 min per episode. These were unrelated to postural changes, urination or defecation. She has hypertension controlled with captopril, metoprolol, and furosemide. On admission, her blood pressure was 140/80 mmHg and heart rate was 62 beats/min. Physical exam was remarkable for a palpable left-sided neck mass. All medications were discontinued. However, she continued to have syncope with sinus bradycardia of 40 beats/min and hypotension with a palpable systolic blood pressure of 70 mmHg. These symptoms resolved after she was given 1 mg of intravenous atropine.

Echocardiogram and electroencephalogram were normal. Computed tomography (CT) scan of the neck revealed a noncalcified 5 × 5 × 13 cm mass involving the left carotid artery and CT of the abdomen showed para-aortic lymphadenopathy. Histopathology of the neck mass revealed diffuse small, non-cleaved, non-Burkitt's, B cell non-Hodgkin's lymphoma. Chemotherapy with cyclophosphamide, adriamycin, vincristine, and prednisone was administered. After one cycle of chemotherapy, her neck mass decreased in size and her bradycardia and hypertension resolved. She completed six cycles of chemotherapy, and repeat CT of the neck, chest, and abdomen showed no evidence of disease.

Three months later she presented with increasing shortness of breath and abdominal distention. She had recurrence of her disease in the neck and abdomen. The patient refused further treatment and expired six weeks later.

Near-syncope is usually encountered in the setting of cardiac disease. A neurologic workup may be prompted by the inability to demonstrate cardiac disease. Near-syncope is rare in the setting of carotid disease and has been best described in carotid sinus hypersensitivity which is usually seen in hypertensive older males with arteriosclerotic disease [1]. It has also been associated with head and neck abscesses, metastatic cervical lymphadenopathy, and primary head and neck malignancies [2,3], but it has never been described in the setting of generalized non-Hodgkin's lymphoma. The neoplasm is thought to produce symptoms by direct compression of the carotid sinus, infiltration of the carotid sinus resulting in increased activity in Hering's nerve and in the parasympathetic arm of the reflex arc, and by inducing a permanent depolarization of the carotid sinus nerve endings thereby lowering their threshold for firing. Unopposed parasympathetic activity is responsible for a transient reduction in cerebral perfusion due to a cardio-inhibitory reflex bradycardia, a vasodepressor response with hypotension, or a combination of the two resulting in near-syncopal symptoms. Immediate therapy focuses on discontinuing medications that can enhance carotid sinus hypersensitivity. Symptomatic patients require atropine, cardiac pacing, or both. Permanent therapy focuses on treating the underlying cause. Chemotherapy and radiotherapy are treatments of choice for head and neck malignancies and generally result in satisfactory resolution of symptoms [4].

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Relapse After Autologous Hematopoietic Stem Cell Transplantation in Acute Myeloid Leukemia, a Single Center Experience Over 13 Years

To the Editor: Autologous hematopoietic stem cell transplantation (AHSCT) has become an important therapeutic option in acute myeloid leukemia (AML) [1,2]. However, the natural history of relapsing patients is poorly described, even in a recent paper focusing on this subject [3]. We would like to report the experience of our institution over a 13-year period to describe the natural history of these patients.

Eighty AML patients (pts) underwent an autologous bone marrow and/or peripheral stem cell transplantation for the treatment of AML. The median age was 37 years (range 11–71), and the sex ratio (M/F) was 1.35. The underlying type of AML in the French-American-British (FAB) classification was M0, 1 pt; M1, 12 pts; M2, 25 pts; M3, 5 pts; M3v, 1 pt; M4, 13 pts; M4e, 7 pts; M5A, 4 pts; M5B, 6 pts; M6, 4 pts; M7, 2 pts. Seventy-two patients had a performance status ≤ 2 (WHO classification). Median leucocyte count was $16.25 \times 10^3/mm^3$. Among the 43 patients with available

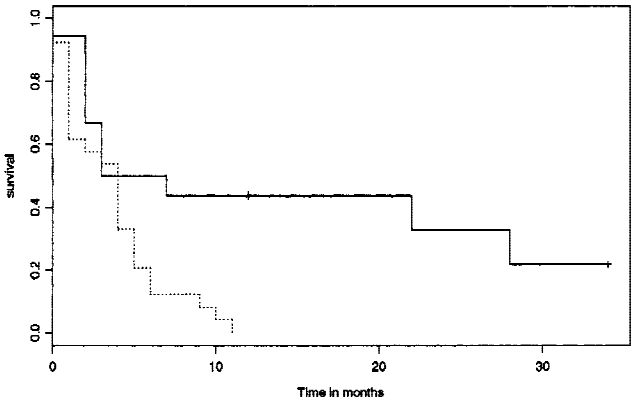

Fig. 1. Survival of the patients (Kaplan–Meier). Full line represents patients relapsing more than 6 months after AP-SCT, and dotted line refers to patients relapsing within these 6 months; *P* = 0.0086 (log-rank test).

karyotype, we detected 8 t(8;21), 5 inv 16, 3 t(15;17), and 17 normal karyotypes. Most of the patients (68) were treated according to ongoing EORTC protocols. Fifty-four patients were autografted in CR1, 19 in CR2, 7 with progressive disease. Seventy-one patients needed only one induction course for CR1. Among the relapsing patients autografted in CR1, 4 needed more than one induction. The conditioning regimen consisted mainly of busulfan treatment (45 pts) or total body irradiation (27 pts). Forty-four patients were autografted with bone marrow (BM), 12 with purged marrow, 19 with peripheral blood stem cells (PBSC), 5 with BM and PBSC.

Forty-four (55%) patients relapsed after AHSCT. The median time to relapse was 4 months [range 1 to 36 months]. Twenty-six patients relapsed within the first 6 months, and 18 patients relapsed after 6 months. Two patients had initial breast and pleura relapse, respectively, with subsequent marrow involvement. Six patients (14%) were treated with supportive care, 6 (14%) with palliative chemotherapy, and 32 (72%) with reinduction chemotherapy. The median survival of the relapsing patients is 3 months with 10% survival at 2 years. Among patients treated with reinduction chemotherapy, 7 (23%) achieved CR, 3 experienced long disease-free survival (12+, 28+, and 34+ months). The only factor influencing survival after relapse was the interval between transplantation and relapse (6 months) ($P = 0.0086$, log-rank test) (see Fig. 1).

Our data confirm the poor outcome of AML relapsing patients as highlighted by Webb. The early relapses after AHSCT are associated with a high toxicity of the reinduction therapy and suggest that high-dose therapy does not overcome drug resistance mechanisms. For patients who relapse before 6 months alternative treatments such as monoclonal antibodies [4] or palliative approach should be considered. Long-term follow-up of patients enrolled in large randomized trials will be of great help in the management of these situations.

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Fludarabine and Risk of Hepatitis B Virus Reactivation in Chronic Lymphocytic Leukemia

To the Editor: Cancer chemotherapy-induced reactivation of hepatitis B virus (HBV) replication with subsequent hepatocellular damage is a well-known complication [1]. We observed two patients with HBs Ag-positive chronic lymphocytic leukemia (CLL) who experienced subacute and chronic hepatic injury while receiving fludarabine-based chemotherapies.

Case 1 was a 57-year-old woman with stage IV CLL. She had normal liver function tests; HBs Ag positive; anti HBe positive; HBV DNA negative. We scheduled fludarabine and cyclophosphamide combination chemotherapy. During this therapy she experienced two HBV reactivation courses which resulted in chemotherapy delays. HBV DNA titers were 843 and 2,000 pg/ml, respectively. The first reactivation resolved spontaneously in 2 months' time. During the second reactivation, liver biopsy showed portal fibrotic expansion and local bridging fibrosis. Famcyclovir therapy, 1.5 g/day, was initiated. A flare up period at the first week of therapy was experienced. Although the hemoglobin and leucocyte counts were stable, a transient thrombocytopenia was observed. At day 10 thrombocyte values returned to famcyclovir pretreatment levels and HBV DNA was 58 pg/ml. At day 30, her performance status was well. Normal ALT and AST levels and negative HBV DNA were noted. The famcyclovir dose was halved. Further chemotherapy was administered without problem, and HBV DNA remained negative during the 5-month follow-up period.

Case 2 was a 59-year-old man with stage II CLL who was given fludarabine as a single agent. After 5 courses of chemotherapy, he presented with ascites and splenomegaly. Laboratory values were consistent with HBV reactivation. HBV DNA was 950 pg/ml. Famcyclovir, 1.5/day, was initiated, but at day 30, the HBV DNA titer was 4,500 pg/ml. Famcyclovir was ceased, and lamuvidine, 300 mg/day, was started.

Fludarabine, the most active single agent for CLL [2], induces a pronounced immunosuppression that often persists for more than a year after therapy [3]. Thus fludarabine therapy further aggrevates immune deficiency in CLL.

HBV is believed to cause hepatocellular injury and necrosis as the result of host immune attack on hepatocytes expressing HBV antigens and/or a direct cytopathic effect [4]. Cytotoxic and immunosuppressive agents permit enhanced HBV replication with an increase in hepatocyte infection. Withdrawal of the agents result in improved immune function which has been associated with acute, subacute, and chronic hepatic injury and hepatic failure [5,6]. Current therapeutic options for HBV infection are in-

terferon-α (IFN-α) and nucleoside analogues. The response to IFN-α treatment in high HBV DNA levels is poor [7]. On the other hand, IFN-α treatment in advanced stage CLL is complicated by disease acceleration, thrombocytopenia, and leukopenia [8]. For these reasons, reactivation of HBV in CLL patients could not be treated with IFN-α. Nucleoside analogues are the most promising treatments for the reactivation HBV infection in immunosupressed patients [6].

In case 1, the patient experienced frequent reactivation periods and chronic hepatic injury which was suppressed by famcyclovir. Especially in case 2 hepatic injury was attributed to direct cytopathic effect of the virus. Since the patient was not in complete remission, fludarabine-induced immunosuppression was long lasting and the HBV DNA titer was still very high 1 month after the recognition of hepatic injury, subacute hepatic injury due to the return of immunocompetence was unlikely.

We believe that reactivation of HBV replication and hepatic injury risk is especially increased for CLL patients on fludarabine-based therapy in comparison with other cytotoxic agents. Patients other than those with CLL being treated with fludarabine-based therapies may have the same risk. These patients need to be closely monitored for reactivation of HBV replication with ALT, AST, and HBV DNA levels. We advocate nucleoside analogs in the setting of HBV reactivation for one year after the cessation of fludarabine-based chemotherapy. Famcyclovir is an effective alternative therapy for reactivation of HBV replication due to cytotoxic chemotherapy. On the other hand, time of reactivation and severity of hepatic injury cannot be predicted. As long as immunosupression continues, prophylactic therapy with nucleoside analogues for HBs Ag-positive patients during cytotoxic or immunosupressive therapy seems logical to prevent irreversible hepatic damage.

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