References

Haematologica vol. 84(11):November 1999

Leukemia and myelodysplasia in patients with essential thrombocythemia treated with cytotoxic agents

Sir,
Essential thrombocythemia (ET) is characterized by increased thrombohemorrhagic risk. Cytotoxic drugs are used in patients at high risk for thrombotic complications, while their use is still debated in low risk patients because of the risk of leukemia or secondary neoplasia. We describe the leukemic risk of available treatments in 187 consecutive patients (66 males and 121 females, mean age 51±17 years) followed in our Department between 1985 and 1997 (median follow up 7 years, SE 2.3). Twenty-three patients received busulfan (BU, 2-4 mg/day), 1 associated with pipobroman (Pi, 25-50 mg/day), 6 radiophosphorus (32P, 74-185 MBq), 48 hydroxyurea (HU, 10-30 mg/kg/day) in 62 cases associated with acetyl salicylic acid (ASA, 100 mg/day). Seventy-seven patients received ASA alone and 33 were not treated. We observed 2 cases of non-lymphoblastic acute leukemia (AL) and 1 of chronic myelo-monocytic leukemia (MDS). No cytogenetic alteration was present in these patients at the time of the diagnosis. One patient evolved into AL after a spent phase, 9 years after the diagnosis of ET. He had been treated with 32P (74 M Bq) and Pi (18,000 mg). The second case of AL, after a spent phase, occurred 10 years after diagnosis of ET treated with BU (132 mg) and HU (414 gr). An 81-year old female was treated with HU (355 mg) and BU (185 mg) for ET and 3 years later developed MDS (Figure 1). They represented 23% of all patients treated with more than 1 cytotoxic agent and 16.6% of 32P treated subjects (incidence rate of AL/MDS in treated patients: 0.6/100 patients/years). The MDS represents 4% of cases of ET over 70 years of age (0.75 case/100 patients/years). No other case of spent phase was registered in our cohort of patients. No cases of AL or MDS were observed in patients without cytotoxic therapy (with or without ASA). Three patients developed cancers (1 colonic, 1 rhino-pharyngeal and 1 gastric). Only in one case did the patient receive 32P (74 M Bq) for ET, the others were under aspirin therapy.

The risk of leukemic transformation in patients treated with 32P appears to be highest between the 5th and 10th years and is usually preceded by a spent phase with myelofibrosis. Our case of AL after 32P therapy has these characteristics.

Figure 1. Individual course of the 3 patients who developed AL (patients ZA and BG) and MDS (BXG).
BU = busulfan, 32P = radiophosphorus, HU = hydroxyurea, Pi = pipobroman, MF = spent phase, AL = acute leukemia, MDS = myelodysplasia.
Crude incidence of MDS varies between 3.5 and 12.6/100,000 patients/year in different studies, while, in the over 70-year-old population an incidence rate of 15-50/100,000 patients/years has been reported; the case of MDS seen in a patient over 70 could, therefore, represent an increased frequency of MDS in ET treated with cytotoxic drugs.

Our study provides no evidence that HU is leukemogenic when used alone: none of the 12 patients treated with HU alone, despite a follow-up longer than 10 years, developed AL. However, HU seems to increase the leukemic risk of other cytoreductive agents. Low doses of ASA are not associated with increased rate of hemorrhages and do not induce leukemic transformation but are able to prevent thrombotic complications totally in all patients (previous published data).

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Key words
Essential thrombocythemia, myelotoxic agents, leukemia, myelodysplasia

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References

Ph+ acute lymphoblastic leukemia after iodine-131 treatment for thyroid cancer

Sir,
The incidence of leukemia after iodine-131 (131I) treatment was not found to be increased in large retrospective observational studies and the risk did not seem to vary according to sex, age or time from exposure.1-2 Leukemia after 131I therapy has been reported in the medical literature to be possible following cumulative dosages of more than 800 mCi, but more recently after a total dose of less than 100 mCi.3,4 We report here the first case of Ph+ acute lymphoblastic leukemia following low dose radioiodine therapy. In January 1986 a 48-year-old Caucasian woman with a papillary thyroid cancer following a total thyroidecmy received 95mCi of 131I and two doses of 100 mCi after 6 and 12 months. In October 1998 she developed fever, diffuse bone pain, severe hyperleukocytosis, anemia, and thrombocytopenia. The bone marrow aspirate and immunophenotype were consistent with a diagnosis of acute lymphoblastic leukemia L1. Cytogenetic analysis showed an abnormal karyotype: 46XX (t9,22)(q34 q11) and the presence of the BCR/ABL rearrangement. The patient was treated with induction chemotherapy but she never achieved complete remission. She was submitted to HLA identical allogeneic transplantation. The patient died of graft-versus-host disease 24 days after transplantation.

Although 131I is known to induce chromosome aberrations, large epidemiologic studies did not find a significant increase in cancer incidence.1-2 In the last decade there have been at least 8 reports describing the occurrence of acute and chronic myeloid leukemia after 131I.3,4,5 The latency from exposure and the occurrence of acute or chronic leukemia were, respectively, 1-3 years and 5-11 years.5 Most of the cases occurred after a cumulative dosage higher than 800 mCi; there are at least 4 reports in the last 2 years concerning acute and particularly CML after small dose of 131I.3,4,5 The involvement of lymphoid lineage seems extremely rare after 131I with only 2 cases having been reported so far.10 Interestingly the small dose of 131I used and the latency observed in our patient are similar to those in patients developing CML after radioiodine. The presence of the p190 transcript is highly specific for Ph+ ALL and progression to a blast crisis of CML in this patient is unlikely. Although we cannot exclude a