The C282Y mutation can be easily and rapidly detected; thus, population screening is feasible. However, because many of those homozygous for this defect will not develop iron overload requiring treatment, the cost effectiveness of widespread population screening requires further evaluation. However, detection of the mutation is useful in confirming the diagnosis in those with increased iron indices.

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A Prospective Study of Radiation Therapy-Associated Thrombocytopenia

To the Editor:

In the April 1, 1997 issue of *Blood*, we reported results from a retrospective study of radiation-associated thrombocytopenia.[1] The primary objective of the study was to identify risk factors for unscheduled interruptions in radiotherapy lasting ≥2 days and associated with World Health Organization grade III-IV thrombocytopenia. A group of controls were randomly selected. Potential risk factors for myelosuppression were analyzed using univariate and multivariate analyses. The most important risk factors for treatment interruption with thrombocytopenia based on multivariate analyses were concurrent chemotherapy (odds radio [OR] 45.5; $P < .001$), increasing percentage of marrow irradiated (OR 4.1 for each 20%; $P < .001$), and brain metastases (OR 7.3; $P = .01$). Other significant ($P < .05$) factors in univariate analyses were leukemia/lymphoma, bone or bone marrow metastases, and prior chemotherapy.

To validate the criteria identified in the retrospective study that were associated with treatment interruptions for thrombocytopenia and to identify new treatment variables that may influence the risk for radiation-induced thrombocytopenia, we performed a prospective study in which we analyzed radiation therapy treatments that were completed between July 6, 1995 and July 29, 1996 at Stanford University Hospital and the Stanford Radiation Oncology facility at Fremont (these dates were selected so that there was no overlap between the retrospective and prospective patient population) and between May 1, 1995 and April 30, 1996 at the Palo Alto Medical Foundation (PAMF). The charts of patients treated at these three facilities were reviewed after completion of the radiotherapy course to identify patients who had unscheduled treatment interruptions of

2 days' duration or more (excluding weekends and holidays) in which thrombocytopenia was the primary reason for interrupting radiotherapy (cases). Patients with ≥grade III thrombocytopenia without unscheduled treatment interruptions and those who received platelet transfusions were also considered to be cases. Patients were identified as high risk (HR) if they were scheduled to receive concurrent chemotherapy with myelosuppressive potential (within 1 day of starting radiotherapy or at any time during the course of radiation therapy) or scheduled to have ≥20% of their bone marrow irradiated, including prior irradiation. Complete information was collected on all HR patients treated at the PAMF and on a random sample of approximately 12 HR patients/month at Stanford (from both Stanford University Hospital and the Stanford Radiation Oncology facility at Fremont). Blood count data including differential and platelet counts were recorded. All patients had at least one complete blood count performed during treatment.

Patient courses rather than patients were sampled, increasing the likelihood of selecting those at HR because of multiple courses. Patient charts were reviewed. Detailed information on the extent of any treatment disruption of ≥2 days and possible predisposing factors for myelosuppression, such as previous or concurrent cytotoxic chemotherapy or previous radiation therapy, was extracted and entered into a computer database for statistical analysis as before. In this study, data were not collected for courses of therapy that consisted only of total body irradiation (TBI), electron beam therapy, brachytherapy, intraoperative radiation therapy (IORT), stereotactic radiosurgery, or therapy for benign disease. Otherwise, all adult patients were eligible for inclusion in this study. All cases had at least one blood count during the treatment course that showed at

least grade I thrombocytopenia. A total of 1,077 patients had records reviewed for inclusion in the study at Stanford and 402 patients had records reviewed for inclusion in the study at the PAMF. The primary analysis tool was logistic regression modeling. Initially parameters were analyzed as univariate predictors. Those that were significant at the $P = .1$ level were considered for inclusion in a multivariate model. Criteria for inclusion in the final model was $P < .05$. In cases in which information on a variable was largely unavailable or if few patients exhibited a characteristic, that variable was excluded from the analysis.

There were 29 patients who met the criteria for being a case at Stanford and 2 cases at the PAMF. These were compared with 148 and 61 HR patients at Stanford and the PAMF, respectively. Because there were only 2 cases at PAMF, all statistical analyses are reported only for Stanford. We determined that all the cases had ≥ 1 risk factor identified in the prior retrospective study, as follows: 27.5% of the cases were on regimens that included concurrent chemotherapy, 58.6% of the cases were scheduled to have $\geq 20\%$ of their total cumulative percentage of bone marrow irradiated, and 31% of cases had known brain metastases. In addition, 20.7% of cases had leukemia or lymphoma, 27.6% had bone metastases, 6.9% had bone marrow involvement, and 51.7% had received prior chemotherapy.

We next sought to determine prospectively whether we could identify additional risk factors for radiation-associated thrombocytopenia within the HR group to improve the specificity of the HR group originally characterized in the retrospective study. Univariate analysis was used to search for significant differences between cases and HR controls. Baseline characteristics and treatment factors that were significantly different for comparisons of cases to the HR group were Karnofsky performance status (lower for cases; $P = .0029$), extent of disease (more advanced in cases; $P = .0432$), brain metastasis (present more often in cases; $P = .0001$), number of prior chemotherapy regimens with myelosuppressive potential administered more than 28 days before radiotherapy (higher in cases; $P = .0011$), and concomitant treatment with drugs (CT) that can affect bone marrow or clotting function (used more frequently in cases; $P = .0185$). The most commonly found CT drugs were nonsteroidal antiinflammatory drugs (NSAID), followed by Dilantin and Bacterium, with 55% of cases and 32% of patients in the Stanford HR group having documentation of CT drugs that could affect bone marrow or clotting function. Those variables that were significant at the $P = .1$ level in the univariate model were entered into a stepwise multivariate model. The final model was based on the presence of brain metastasis (OR 8.9; $P < .001$) and the number of prior chemotherapy regimens with myelosuppressive potential (increase in OR of 1.8 per additional regimen; $P = .01$).

In this study, we, therefore, (1) validated the criteria identified in the retrospective study (concurrent chemotherapy, $\geq 20\%$ of active bone marrow irradiation, and brain metastases) that were associated with thrombocytopenia, and (2) identified the number of prior chemotherapeutic regimens with myelosuppressive potential as being a significant ($P = .01$) predictor of thrombocytopenia in a stepwise multivariate analysis. However, it is clear that differences in patient populations and patterns of care at given institutions will influence the likelihood that patients will experience clinically significant thrombocytopenia. PAMF is a community-based practice and Stanford University Hospital is a tertiary referral center that treats more complex and advanced cases (patients with regional disease) and more frequently uses concurrent myelosuppressive chemotherapy than the PAMF. Therefore, PAMF had only 2 cases compared with 29 cases in a year at Stanford, although the PAMF treats approximately one third as many patients per year as Stanford.

The findings reported here make it possible to prospectively iden-

tify radiation therapy patients at increased risk for clinically significant radiation-induced thrombocytopenia. In addition, since the discovery of the Mpl ligand,[2-4] there is now the prospect of effective treatment or prevention of chemotherapy[5] and radiotherapy-induced thrombocytopenia with megakaryocyte colony-stimulating factor. This information has implications for both the practice of clinical medicine and the future design of studies looking at the potential utility of using a platelet growth factor (eg, MGDF) in patients at HR of radiation-induced thrombocytopenia.

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