

## Solid-Tumor Second Cancer Risk High for Stem Cell Transplant Recipients

A Canadian study showed that patients who undergo myeloablative allogeneic hematopoietic stem cell transplantation (allo-HSCT) for hematologic malignancies have an 85% increased risk of developing a second, solid malignancy later in life. The researchers looked at the records of 926 patients who underwent myeloablative allo-HSCT for a variety of hematologic malignancies over 18 years. It was found that 28 patients developed 30 solid-tumor malignancies at a median of 6.8 years following allo-HSCT. The 10-year cumulative incidence was 3.1%, but it was 2.3% when nonmelanoma cancer of the skin and in situ cancer of the cervix were excluded from the calculation. Relative risk of second, solid neoplasm was found to be quite high in patients age 40 or over at the time of transplantation, at 4.75. Furthermore, relative risk was 3.83 for those who received stem cells from a female donor; this observation was characterized by the researchers as unexpected. Among men who received stem cells from a female donor, the relative risk was increased by 4.7 in comparison to men who had received the stem-cell donation from another man. The age- and sex-adjusted relative risk of a second, solid-tumor cancer after transplantation was 1.85 in comparison to the general population of British Columbia, Canada. Second cancers most commonly reported were basal and squamous cell carcinomas, followed by cancers of the lung, oral cavity, colon, and bladder. The researchers note that extended follow-up in this population is necessary to more fully assess the incidence of second cancers, which continues to increase with time.

## Imatinib More Effective in Chronic Leukemia Than Previous Standard Therapy

A prospective study of imatinib (Gleevec, Novartis), which inhibits the *BCR-ABL* tyrosine kinase, as an initial and continued therapy for chronic myeloid leukemia (CML) showed a 5-year overall survival rate of 89%, which was better than interferon alfa plus cytarabine, the former standard of care in this setting for patients not planning to undergo hematopoietic stem-cell transplantation. The survival rate seen with imatinib was notable because it was the highest rate ever published based on a prospective study of therapy for CML. In the December 7, 2006, issue of the *New England Journal of Medicine*,

Dr. Brian J. Druker and colleagues reported the outcomes of 553 patients who were initially randomized to receive imatinib and an equal amount of patients to interferon alfa plus cytarabine over a median follow-up period of 60 months. Of the patients who received interferon alfa plus cytarabine, 359 crossed over to imatinib. It was found that the complete cytogenetic response rates for imatinib-treated patients were 69% and 87% by 12 and 60 months, respectively. Approximately 7% of patients progressed to accelerated-phase CML or blast crisis. Among patients found to have a complete cytogenetic response or in whom levels of *BCR-ABL* transcripts had fallen by at least 3 log, a significantly lower risk of disease progression was found as compared to patients without a complete cytogenetic response ( $P < 0.001$ ). Over time, rates of grade 3 and 4 adverse events decreased, with no relevant changes observed in the profiles of these adverse events. It is thus believed that initial therapy and continuous treatment with imatinib for chronic-phase CML will produce durable responses in most patients.

## Gemcitabine Plus Carboplatin Has Comparable Efficacy and Less Toxicity as Compared to Standard Paclitaxel-based Regimens in Ovarian Cancer

A combination of gemcitabine and carboplatin given to chemotherapy-naive ovarian cancer patients was found to be associated with comparable rates of response and a more acceptable toxicity profile than the commonly used combination of paclitaxel and carboplatin. In a phase II study reported by researchers from Singapore in the December issue of *BJOG: An International Journal of Obstetrics and Gynecology*, 20 previously untreated women with stage IIIc and IV ovarian cancer were administered gemcitabine intravenously (1000 mg/m<sup>2</sup> on days 1 and 8) and carboplatin (area under the curve = 5 on day 1) every 3 weeks for six cycles. Among these women, 16 completed all six cycles, 1 completed five, and 1 completed four. Subjects who received more than three cycles were eligible for evaluation; thus, the overall response rate observed was 83.3% and the clinical complete response rate was 61%. These rates were considered comparable to those seen with first-line paclitaxel-carboplatin or paclitaxel-cisplatin combination chemotherapeutic regimens. Additionally, median overall survival rates were considered comparable to combinations containing paclitaxel and platinum at 29.2 months after a median follow-up of 38.7 months.

Median progression-free survival was 11.6 months. All 20 patients were assessed for toxicity. The combination of gemcitabine and carboplatin was associated with World Health Organization (WHO) grade 3 anemia, neutropenia, and thrombocytopenia in 7.65%, 9.5%, and 0% of patients on day 8, and 15.5%, 12.2%, and 15.5% of patients on day 15, respectively. It was noted that 2 women required a total of three hospital admissions for neutropenic sepsis, and 2 required five hospital admissions for platelet transfusions for severe thrombocytopenia. Nausea, vomiting, and skin rashes were found to be mild and infrequent, and peripheral neuropathy was not observed in any patients. World Health Organization grade 1 alopecia was seen in all 20 patients. In contrast, a recent study of a combination of cisplatin and gemcitabine in a similar cohort demonstrated grade 3 nausea and vomiting in 25.6% of patients but alopecia in only 9.5%. Paclitaxel combined with carboplatin, in comparison, is associated with grade 4 alopecia and flushes in nearly all patients and peripheral neurotoxicity in approximately one third of patients. Despite the success of this gemcitabine-carboplatin combination regimen, the authors note that advanced ovarian cancer remains incurable. As a result, minimizing adverse effects of therapy is of great importance.

### Two Trials of Trastuzumab in HER2-positive Breast Cancer Show Promising Results

Interim results from a phase III study of trastuzumab (Herceptin, Genentech) in combination with chemotherapy in early-stage human epidermal growth factor 2 (HER2)-positive breast cancer showed improved disease-free survival with the addition of trastuzumab to chemotherapy in comparison to chemotherapy alone. Trastuzumab targets the overexpression of HER2, which is associated with aggressive breast cancer, poor prognosis, likely recurrence, and decreased survival. In this trial, women received a combination chemotherapeutic regimen of doxorubicin and cyclophosphamide followed by docetaxel or the same chemotherapeutic regimen followed by docetaxel and trastuzumab or docetaxel, carboplatin, and trastuzumab. Over 3,000 women with early-stage HER2-positive breast cancer were enrolled in the trial. Both the arms containing trastuzumab resulted in improved disease-free survival as compared to the chemotherapy-alone arm. An analysis of overall survival during a median 36-month follow-up showed that the arm that used chemotherapy followed by docetaxel and trastuzumab had a 41% reduction in the risk of death (hazard ratio [HR] = 0.59) and the arm that used docetaxel, carboplatin, and trastuzumab had a 34%

reduction in the risk of death (HR = 0.66). This trial was additionally notable for exploring the use of trastuzumab in node-negative patients, in a regimen that did not contain anthracyclines, in combination with docetaxel, and in a once-every-3-week schedule. Because anthracyclines were not used, rates of congestive heart failure were similar in the control arm and the docetaxel, carboplatin, and trastuzumab arm. These results were reported at the San Antonio Breast Cancer Symposium in December 2006.

A second phase III trial evaluating HER2-positive breast cancer treated with trastuzumab was also presented. In this trial, patients' tumors were HER2-positive and hormone receptor-positive, and their breast cancer was metastatic. Two-hundred-seven patients received either an aromatase inhibitor (anastrozole) plus trastuzumab or anastrozole alone. Median progression-free survival in the trastuzumab-plus-anastrozole arm was double that in the anastrozole-alone arm (4.8 vs 2.4 months). The most common adverse events in the combination arm were fatigue, diarrhea, vomiting, fever, nausea, and nasopharyngitis. Thirteen patients in the combination arm experienced cardiac dysfunction, but only 2 experienced this adverse event in the anastrozole-alone arm.

#### In Brief

**Patients who have received chemical or thermal burns are not at increased risk of developing skin cancers** later in life, contrary to some earlier reports. One possible explanation is that sun exposure is lessened in this population due to discomfort associated with such exposure. (*Epidemiology*. 2006;17:668-673.)

**Obese women and women with a comparatively low socioeconomic status are less likely to receive full doses** of adjuvant chemotherapy for breast cancer, according to a study of 764 patients treated with a standard regimen of chemotherapy for stage I, II, or III breast cancer. Further research is needed to determine if the reduced doses observed are tied to worse outcomes. (*J Clin Oncol*. 2007;25:277-284.)

**Electromagnetic fields produced by cellular phones are not associated with increased risk of leukemia** or tumors of the brain/nervous system, salivary gland, or eye, according to an epidemiologic study of Danish cell phone users from 1982 to 1995. Gliomas occurring in the temporal and parietal lobes, closest to a cellular phone's antenna, were not found to be more likely among this cohort than the general population. (*J Natl Cancer Inst*. 2006;98:1707-1713.)