There has been a remarkable explosion in medical information over the past several years. The rate of new discoveries and improved understanding of the biology and treatment of cancer is ever-increasing. The same is true in the area of supportive cancer therapy.[1]

In the area of medical oncology we have been confronting the problem of neutropenia related to myelosuppressive chemotherapy treatment for decades. Prior to the 1990s, our only approach was to educate chemotherapy patients about the risk of neutropenia, monitor their blood counts periodically, and aggressively manage neutropenia-related fever and infection.[2,3] Because of the morbidity and mortality associated with these neutropenic events, patients who recovered adequately to undergo further therapy generally received chemotherapy dose reduction. This strategy was also used as a primary approach at the initiation of therapy for patients for whom the oncologist was concerned that the risks and/or consequences of development of neutropenia and infection might outweigh the benefits of full-dose treatment. Treatment alternatives to change this paradigm first occurred in 1991, with the clinical approval of the colony-stimulating factors. The use of colony-stimulating factors as primary prophylaxis after myelosuppressive chemotherapy allowed patients to reduce their risk of neutropenic complications.[3] These agents also provided an opportunity to try to maintain full-dose chemotherapy in patients who had experienced a neutropenic event on a prior chemotherapy cycle. However, over the past decade, the strategy of secondary prophylaxis has been frequently employed due to the limitations in our understanding of individual patient risk. Primary prophylaxis has also been limited by the American Society of Clinical Oncology (ASCO) guidelines. Most studies demonstrating benefit have been performed in the setting of very-high-risk chemotherapy regimens where the expected incidence of febrile neutropenia was in excess of 40%. Since most chemotherapy regimens that are standard in clinical practice have a substantially lower risk of febrile neutropenia, and because our patient risk models have not been well developed, the reactive approach for use of colony-stimulating factors has been the norm. The results of this "watch and wait" approach for the supportive management of neutropenia are clearly seen in several of the abstracts from the ASCO 40th Annual Meeting and the Multinational Association for Supportive Care in Cancer (MASCC)/International Society for Oral Oncology (ISOO) 16th International Symposium, both held earlier this year. The frequency of neutropenia in clinical practice remains alarmingly high, and the complications in terms of inpatient hospitalization, morbidity, mortality, and economic cost from the University HealthSystem Consortium database is staggering. In 2002, a second-generation granulocyte colony-stimulating factor (pegfilgrastim [Neulasta]) was approved for use in the prevention of chemotherapy-related neutropenia. Clinical benefit from a single injection postchemotherapy was equivalent to that of daily dosing for more than 10 days of filgrastim (Neupogen) in randomized trials.[4] In addition to the advantages of improved technology and better patient and provider convenience, subsequent clinical trials have not only helped us better understand the utility of pegfilgrastim, but also helped us refine our use of colony-stimulating factors. Included in the 2004 ASCO/MASCC abstracts are important prospective studies that evaluate the benefits of filgrastim or pegfilgrastim in primary prevention of neutropenic complications in patient populations receiving chemotherapy where the risk of febrile neutropenia is substantially less than 40%. As the reader will see in the pages ahead, risk reduction may be even greater in these lower-risk myelosuppressive settings. In addition to improving our understanding of the epidemiology of neutropenia and its consequences and the ability to redefine our threshold of primary prophylaxis with colony-stimulating factors, the 2004 ASCO and MASCC/ISOO abstracts also provide a wealth of information in the disease-specific areas of breast cancer, lung cancer, lymphoma, and hematologic malignancies. I invite the reader to review all of the sections carefully to better refine your understanding of the prevention and management of neutropenia in cancer chemotherapy patients within your own practice. In 2005 the ASCO guidelines will be updated, and we will see for the first time the National Comprehensive Cancer Network guidelines on the use of...
Assessing the Risks and Consequences of Neutropenia

Abstract #6125

Risk of Neutropenic Complications Based on a Prospective Nationwide Registry of Cancer Patients Initiating Systematic Chemotherapy

D. A. Wolff, J. Crawford, D. C. Dale, M. S. Poniewierski, G. H. Lyman, for the ANC Study Group University of Rochester Medical Center, Rochester, New York; Duke University Medical Center, Durham, North Carolina; University of Washington Medical Center, Seattle, Washington

Myelosuppression represents the major dose-limiting toxicity of cancer chemotherapy. A prospective, nationwide study was undertaken to define risk factors for neutropenic complications (NC) and to develop risk models for selecting patients for hematopoietic support. More than 2,500 patients have been prospectively registered at 137 randomly selected practice sites. Primary outcomes included documented severe neutropenia (SN) (ANC < 500), NC (fever/infection/other), and severe neutropenic events (SNE) (SN or NC). This preliminary analysis is based on the first 2,222 patients treated to date including 886 (40%) age ≥ 65. One-third did not receive at least four cycles of chemotherapy due to disease progression (55%), refusal (11%), death (11%), and unknown (23%). Neutropenia (ANC < 1,000) was documented in 40%, including SN in 26%. More than one-half of all initial events occurred during cycle 1. In addition to cancer and regimen type, significant predictors of SN included gender (.001), baseline neutrophils (.01), diabetes (.037), and chronic lung disease (.001). Significant predictors of NC included gender (.004) and stage (.04). In addition to cancer and regimen type, significant predictors of SNE included gender (.004) and stage (.04). In addition to cancer and regimen type, significant predictors of SNE included gender (.004) and stage (.04). The risk of SNE in all cycles (first cycle) includes breast 49 (36), lung 31 (20), lymphoma 42 (33), ovary 37 (17), and colon 18 (8). See Table 1 for summary.

CONCLUSION: Neutropenic complications and severe neutropenic events occur early in the course of therapy, potentially compromising chemotherapy dose intensity and clinical outcomes. Significant independent risk factors include cancer type, regimen, dose intensity, gender, stage, and several comorbidities. Abstract #A-29

Assessment of Neutropenic Risk in Cancer Patients Receiving Systemic Chemotherapy: Results From a Prospective Nationwide Registry


Myelosuppression, including chemotherapy-induced neutropenia (CIN), is the major dose-limiting toxicity of cancer chemotherapy. This prospective, nationwide study was undertaken to better define risk factors for CIN in treatment-naive or previously treated patients with five major tumor types (breast, lung, colon, ovarian, and lymphoma). More than 2,500 patients initiating a chemotherapy regimen have been prospectively registered at 137 randomly selected practice sites. Primary outcomes include severe neutropenia (SN; ANC < 500), neutropenic complications (NC; fever/infection/other), and severe neutropenic events (SNE; SN or NC). Of the first 2,222 patients enrolled, 886 (40%) were > 65 years of age. One-third of patients received fewer than four cycles of chemotherapy due to disease progression (55%), refusal (11%), death (11%), or other unknown reasons (23%). Neutropenia (ANC < 1,000) and severe neutropenia were documented in 40% and 26% of patients, respectively. Neutropenic complications occurred early in the course of treatment in all tumor types, with 67% of all SNE in cycle 1. The risk of SNE (all cycles; first cycle) varied greatly
with disease: breast (49%; 36%), lung (31%; 20%), lymphoma (42%; 33%), ovary (37%; 17%), colon (18%; 8%). In addition to tumor type and treatment regimen, significant predictors (P value) of SNE included gender (.001), baseline neutrophils (.01), and comorbidities including diabetes (.037) and chronic lung disease (.001). Significant predictors of NC included female gender (.004) and stage (.04) with borderline significance for previous neutropenia and comorbidities. In addition to cancer and regimen type, significant predictors of SNE included female gender (.006), stage (.007), and chronic lung disease (.029), with borderline significance for baseline white blood cell and neutrophil count. CONCLUSION: This prospective registry holds promise for the development of a reliable, generalized risk model that will allow the accurate prediction of neutropenic risk in individual patients, enabling the selection of patients who may benefit from prophylactic hematopoietic support. Abstract #6049

Complications and Costs Associated With Febrile Neutropenia in Hospitalized Adult Cancer Patients N. M. Kuderer, J. Crawford, D. C. Dale, G. H. Lyman, for the ANC Study Group University of Rochester Medical Center, Rochester, New York; Duke University Medical Center, Durham, North Carolina; University of Washington Medical Center, Seattle, Washington Fever in the setting of neutropenia (FN) frequently requires hospitalization for empiric broad-spectrum antibiotics. More complete understanding of the medical complications and costs associated with hospitalization for FN is needed. Hospitalization of cancer patients with FN at 115 academic medical centers between 1995 and 2000 was studied using the discharge database of the University HealthSystem Consortium. Primary outcomes included length of stay (LOS), cost, infectious complications, and mortality. Logistic regression analysis was used to estimate relative risk based on adjusted odds ratios (OR). Hospitalization with FN was reported in 41,779 adult cancer patients. Mean (median) LOS was 11.2 (6) days while the average (median) cost was $19,110 ($8,376) per episode. The 35% of patients hospitalized ≥ 10 days accounted for 74% of hospital days and 78% of total cost. Over the 6 years of observation, LOS decreased 10% while cost per day and total cost increased 28% and 13%, respectively. Documented infection was reported in 38% of patients including sepsis in 19% and pneumonia in 10%. Death during hospitalization was reported in 11% of admissions. Mortality was most commonly associated with gram-negative sepsis (34%), pneumonia (27%), or comorbidities including renal (30%), cerebrovascular (30%), liver (28%), and lung disease (27%). Mortality rates increased with the number of comorbidities (P trend < .001). Odds ratios for death were as follows: gramnegative sepsis (4.8), pneumonia (2.4), renal (3.1), cerebrovascular (3.2), liver (2.9), and lung disease (3.9). Odds ratios for complicated hospitalization (length of stay ≥ 10 days) were leukemia (3.4), grampositive sepsis (2.5), and comorbidities with lung (2.1), renal (2.1), cerebrovascular (2.1), and liver disease (2.0) after adjustment for other comorbidities and infectious complications. CONCLUSION: Hospitalization for FN is associated with considerable morbidity and mortality. Numerous patient characteristics, comorbidities, and infectious complications are associated with increased mortality, length of stay, and cost. Abstract #A-57

Adult Cancer Patients Hospitalized With Febrile Neutropenia: Risk Stratification Based on an Analysis of the University HealthSystem Consortium Discharge Database N. M. Kuderer, J. Crawford, D. C. Dale, G. H. Lyman for the ANC Study Group University of Rochester, Rochester, New York; Duke University, Durham, North Carolina; University of Washington, Seattle, Washington Febrile neutropenia (FN), the major dose-limiting toxicity of cancer chemotherapy, frequently requires hospitalization for the administration of empiric broad spectrum antibiotics. For a better understanding of the clinical impact and economics of hospitalization for FN, the records of 41,779 adult nontransplant cancer patients admitted with FN at 115 academic medical centers between 1995 and 2000 were analyzed using the discharge database of the University HealthSystem Consortium. Primary outcomes included length of stay (LOS), cost, infectious complications, and mortality. Average age was 53.6 years with 28% ≥ 65 years. Mean (median) LOS was 11.2 (6) days while the average (median) cost was $19,110 ($8,376) per episode. The 35% of patients hospitalized for ≥ 10 days accounted for 74% of hospital days and 78% of total cost. Documented infection and death during hospitalization were reported in 38% of patients and 11% of admissions, respectively. Mortality rates increased with the number of comorbidities (P-trend < .0001). In multivariate analysis, risk factors (odds ratios) for inpatient mortality were gram-negative sepsis (4.84), pneumonia (2.33), and renal (3.19), cerebrovascular (3.29), liver (2.93), and lung disease (3.95); predictors for LOS ≥ 10 days were grampositive sepsis (2.39), leukemia (3.54), and various comorbidities. Risk scores for LOS ≥ 10 days (range: 0-32) and inpatient mortality (range: 0.34) were derived from the logistic regression models. These risk scores effectively discriminated patients at high risk for prolonged hospitalization with FN and inpatient mortality. The 24% of patients with risk scores > 4 experienced a risk of ≥ 50% for LOS ≥ 10 days. Similarly, the 27% of patients with risk
scores > 5 experienced a risk of ≥ 12% for inpatient mortality. CONCLUSION: By identifying individual cancer patients at increased risk for prolonged hospitalization and inpatient mortality, the risk score analysis may help guide supportive care treatment decisions, improve outcomes, and potentially reduce the cost of cancer care. **Abstract #6060**

**Human Resource Costs and Patient Time Affected By the Delivery of Chemotherapy and Neutropenia Management**

B. V. Fortner, T. A. Okon, L. Zhu, K. Tauer, K. Moore, D. Templeton Supportive Oncology Services, Memphis, Tennessee; The West Clinic, Memphis, Tennessee

The purpose of this study was to evaluate human resource costs and patient time associated with the delivery of chemotherapy and management of chemotherapy-induced neutropenia (CIN). A total of 400 medical professionals were surveyed regarding human resource time associated with medical tasks, and 189 patients were surveyed regarding time and activities affected by medical visits across 20 community oncology practices. Results [mean (standard deviation)] showed chemotherapy and CIN-related medical visits involve numerous types of professionals (X = 10 per practice) who execute multiple medical tasks (X = 230 per practice), resulting in substantial human resource time and expense to the practice. For example, 1 day of chemotherapy X = 4.23 (1.48) hours, $152.55 ($65.89); midcycle lab visit X = 2.09 (1.05) hours, $48.62 ($28.22); 5 days of IV antibiotics X = 15.7 (6.1) hours, $415.9 ($213.6); 10 days of filgrastim X = 24.4 (11.1) hours, $579.30 ($292.60); 1 day of pegfilgrastim X = 2.40 (1.12) hours, $57.06 ($30.94). Furthermore, results showed that even relatively simple medical visits resulted in large disruptions of patient time and life activities before, during, and after the visit. For example, 1 day of chemotherapy X = 8.19 (3.93) hours; midcycle lab visit X = 2.27 (0.92) hours; 5 days of IV antibiotics X = 16.31 (4.92) hours; 10 days of filgrastim X = 23.2 (9.01) hours; 1 day of pegfilgrastim X = 2.36 (1.44) hours. Sensitivity analysis demonstrated that as rates of severe CIN increase, human resource costs and patient burden increase. At relatively high rates of CIN, prophylactic use of growth factors was predicted to be less burdensome to patients and more cost-effective in terms of human resource costs. CONCLUSION: These data are important for understanding the cost implications of delivering chemotherapy in the community oncology setting. These data are also important for understanding the burden multiple medical visits place on patients and their caregivers and may help guide the creation of supportive care strategies that minimize unnecessary patient and caregiver burden. **Commentary on Abstracts #6125, #A-29, #6049, #A-57, and #6060**

Jeffrey Crawford, MD To understand the magnitude of complications of chemotherapy, in the past we have relied on the results of clinical trials. Unfortunately, results of these trials led us to underrate the severity and magnitude of neutropenia for several reasons. First and most importantly, the clinical trials were done in a selected population of patients of generally better performance status, younger age, and with less prior treatment, and therefore were often not comparable to clinical practice. In addition, even phase III trials were uneven with reference to laboratory monitoring and reporting of neutropenic events. Therefore, the best way to understand the true magnitude of neutropenia and to identify patients at risk is through population-based databases. Perhaps one of the most important studies to assess the magnitude of neutropenia in community practice is the ongoing prospective nationwide registry of cancer patients initiating systemic chemotherapy as reported by the ANC study group (ASCO abstract #6125 and MASCC abstract #A-29). At the times of these reports more than 2,500 patients had been prospectively registered from 137 randomly selected practice sites. Forty percent of the population is over the age of 65. Neutropenia occurred in 40% of the patients and severe neutropenia in 26%. More than half of all the initial neutropenic events occurred in the first cycle of treatment, speaking to the problem of the "watch and wait" approach. At the time of this analysis, risk factors for severe neutropenia varied by tumor type and treatment regimen, but also included female gender, stage, and comorbidity, particularly lung disease. As this registry is completed, it is hoped that a prospective risk model can be developed for validation in subsequent trials. Equally impressive from the ANC study group reported by Kuderer and colleagues (ASCO abstract #6049, MASCC abstract #A-57) are the results of a retrospective analysis of the University HealthSystem Consortium (UHC) discharge database. This administrative database provided records on more than 40,000 adult nontransplant cancer patients who were admitted with febrile neutropenia at 115 academic medical centers between 1995 and 2000. While the median length of stay for febrile neutropenia was 6 days, the mean number of days was 11, and 35% of patients were hospitalized for 10 days or longer. This 35% of patients accounted for 78% of the total cost. Documented infections occurred in 38% of patients and 11% of patients died during hospitalization- alarmingly high numbers. Mortality rates were clearly related to the number of comorbidities as outlined in the abstract. Better understanding of the population of patients who not only have experienced febrile neutropenia, but have experienced the worst
complications, may also help refine prospective risk models. Another interesting abstract presented at ASCO by Fortner and colleagues (ASCO abstract #6060) looked at human resources and patient time affected by neutropenia management. Even in the absence of severe complications such as hospitalization, the time spent for simple medical visits and disruption of patient time and life activities was substantial for the patient and caregiver. Equally important was the impact on the oncologist’s office practice. Such analyses are important if we are to truly measure the economic and personal costs involved with neutropenia management. **Redefining the Febrile Neutropenia Risk Threshold Abstract #8002**

**Prevention of Chemotherapy-Induced Febrile Neutropenia by Antibiotics vs Antibiotics Plus Granulocyte Colony-Stimulating Factor in Small-Cell Lung Cancer: A Randomized Phase III Study**

J. Timmer-Bonte, B. Biesma, J. Smit, F. Wilschut, J. Akkermans, T. De Boo, G. Bootsma, V. C. Tjan-Heijnen University Medical Centre Nijmegen, Nijmegen, Netherlands; Jeroen Bosch Hospital, Den Bosch, Netherlands; Rijnstate Hospital, Arnhem, Netherlands; Gelderse Vallei Hospital, Ede (Gld), Netherlands Supported by a research grant from the Dutch Healthcare Insurance Board Febrile neutropenia (FN) is a major complication of chemotherapy in patients with small-cell lung cancer (SCLC). Granulocyte colony-stimulating factor (G-CSF) is used to prevent FN, but its primary use is only recommended in patients with a considerable (> 40%) risk of FN (ASCO guidelines, *J Clin Oncol* 2000). Antibiotics are also effective in preventing FN, even reduce infection-related mortality, and are cost-effective (Tjan-Heijnen VC: *Ann Oncol* 2001). In this multicenter randomized phase III trial, the role of combined primary prophylaxis with antibiotics plus G-CSF in patients with SCLC at increased risk of FN was determined. Patients with SCLCLimited disease and performance status (PS) 2/3, or age over 60 years or judged not suitable for concurrent chemo/radiotherapy, and patients with SCLCextensive disease were considered at increased risk of FN. Patients were stratified for age (< / ≥ 60 years), PS (0-1/2), extent of disease (limited/extensive), and line of therapy (first/second), and randomized for primary prophylaxis with antibiotics (ciprofloxacin 500 mg + roxithromycin 150 mg, bid, days 4-13) alone or in combination with G-CSF (filgrastim 5 μg/ kg/days 4-13). Chemotherapy consisted of cyclophosphamide 1,000 mg/m² day 1, doxorubicin 45 mg/ m² day 1, and etoposide 100 mg/m² days 1, 2, 3, IV q3wk, * 5. The primary end point was incidence of FN in first cycle. Targeted accrual was N = 156 patients (78/arm). See Table 1 for results. A total of 171 patients were eligible. Patient characteristics were well balanced.

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>AB</th>
<th>AB + G-CSF</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC x 10⁹/L &lt; 0.5</td>
<td>54 (72%)</td>
<td>46 (53%)</td>
<td>.0129</td>
</tr>
<tr>
<td>N = 75</td>
<td>N = 86</td>
<td></td>
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<tr>
<td>FN first cycle</td>
<td>19 (23%)</td>
<td>9 (10%)</td>
<td>.0270</td>
</tr>
<tr>
<td>N = 75</td>
<td>N = 79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FN subsequent cycles</td>
<td>12 (16%)</td>
<td>9 (11%)</td>
<td>.3025</td>
</tr>
<tr>
<td>N = 75</td>
<td>N = 79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FN overall</td>
<td>24 (30%)</td>
<td>16 (18%)</td>
<td>.037</td>
</tr>
<tr>
<td>N = 171</td>
<td>N = 175</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FN-related mortality</td>
<td>6 (7%)</td>
<td>3 (3%)</td>
<td>.248</td>
</tr>
</tbody>
</table>

CONCLUSION: The addition of primary prophylactic G-CSF to prophylactic antibiotics significantly reduced the incidence of chemotherapy-related FN in SCLC patients at increased risk of FN, especially in the first cycle by 50%. **Abstract #620**

**Prophylactic Growth Factor Support With Adjuvant Docetaxel, Doxorubicin, and Cyclophosphamide for Node-Negative Breast Cancer: An Interim Safety Analysis of the GEICAM 9805 Study**

M. Martin, A. Lluch, M. A. Segu, A. Antx, A. Ruiz, M. Ramos, A. Rodriguez-Lescure, E. Adrover Spanish Breast Cancer Research Group (GEICAM), Madrid, Spain For patients with node-negative breast cancer, TAC (docetaxel, doxorubicin, and cyclophosphamide) confers significant disease-free and overall survival benefits vs FAC (fluorouracil, doxorubicin, cyclophosphamide), but with a higher rate of febrile neutropenia (Martin M: SABCS 2003, abstract...
In our study of TAC vs FAC for node-negative breast cancer, we performed an interim safety analysis to assess the impact of growth factor support on the incidence of TAC-related adverse events. Following surgery, patients with operable, high-risk (St Gallen, 1998), node-negative breast cancer, 18-70 years old, Karnofsky performance status ≥ 80%, and adequate hematologic and organ function were randomized to FAC (F 500 mg/m², A 50 mg/m², C 500 mg/m²) or TAC (T 75 mg/m², A 50 mg/m², C 500 mg/m²) day 1 q3wk for six cycles. After enrollment of 224 patients, the study was amended to require prophylactic G-CSF for patients subsequently treated with TAC, but not FAC. The present analysis assessed the impact of G-CSF on the incidence of febrile neutropenia (FN; fever ≥ grade 2 with grade 4 neutropenia) and other grade 3/4 toxicities in patients treated with TAC. At the cutoff date for this analysis, 448 patients had been enrolled: 124 received FAC (111 prior to amendment) and 124 TAC (109 without mandatory G-CSF [TAC-G]; 115 with G-CSF [TAC+G]). For patients receiving FAC, the incidence of FN (% patients) was 1.3% (0.9% pre-, 1.7% postamendment); other grade 3/4 adverse events were observed in 26.7% (27% preand 26.5% postamendment). Among patients treated with TAC, the rates of febrile neutropenia were 23.8% for TAC-G (95% CI = 15.9%-31.9%) and 3.5% for TAC+G (1.0%-8.7%); the rates of other grade 3/4 toxicities were 50.4% for TAC-G (41.1%-59.8%) and 20% for TAC+G (12.7%-27.3%). The relative dose intensities for TAC-G vs TAC+G, respectively, were T: 92% vs 96%, A: 93% vs 97%, C: 93% vs 97%. CONCLUSION: Within the limitations of a nonrandomized comparison, the use of G-CSF beginning with the first cycle of TAC substantially reduces the incidence of FN and other grade 3/4 toxicities and enables maintenance of chemotherapy dose intensity for women with early stage breast cancer. The adverse event rate with TAC + G is similar to that of FAC. Abstract #A-52

**Prophylactic Pegfilgrastim Significantly Reduces the Incidence of Febrile Neutropenia, Hospitalizations, and IV Anti-Infective Use in Patients With Breast Cancer Receiving Docetaxel: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study L. Schwartzberg, S. Tjulandin, M. Wijtkiewicz, L. J. Barajas-Figueroa, M. Palmer, T. Neumann West Cancer Clinic, Memphis, Tennessee; Blokhin Cancer Research Center, Moscow, Russia; Regional Oncology Centre, Białystok, Poland; Hospital General de Occidente, Zapopan, Jalisco, Mexico; Amgen Inc, Thousand Oaks, California Previous studies have demonstrated that once-per-cycle pegfilgrastim (Neulasta) is as effective as daily filgrastim (Neupogen) for the reduction of febrile neutropenia (FN) in patients with breast cancer receiving chemotherapy regimens associated with a high risk of FN. Current treatment guidelines recommend prophylactic use of colony-stimulating factors for treatment regimens associated with a ≥ 40% incidence of FN. To test whether patients at moderate risk of FN may also benefit from once-per-cycle, first-cycle use of pegfilgrastim, this phase III randomized, doubleblind, placebo-controlled study evaluated the effects of prophylactic, fixed doses of pegfilgrastim on the incidence of FN in patients with breast cancer receiving docetaxel; which is associated with an average reported FN incidence of 20% in the absence of growth factor support. Patients with breast cancer (stage II to IV) and an ECOG performance status of 0 to 2 who were candidates for docetaxel chemotherapy (100 mg/m² every 3 weeks) were eligible for participation. Patients were randomized in a 1:1 allocation to receive either 6 mg of pegfilgrastim or placebo once per cycle on the day after docetaxel administration for up to four cycles. Febrile neutropenia was defined as a temperature ≥ 38.2°C and absolute neutrophil count (ANC) < 0.5 * 10⁹/L (measured on the same day or the day after a temperature ≥ 38.2°C). A total of 928 patients were randomized to receive pegfilgrastim (n = 463) or placebo (n = 465). The percentage of patients developing FN was statistically significantly lower in the pegfilgrastim group (1% [6/463]) compared with the placebo group (17% [78/465]; P < .0001). Pegfilgrastim was also associated with a significantly lower incidence of hospitalizations (1% [6/463] vs 14% [64/465]; P < .0001) and intravenous anti-infective use (2% [7/463] vs 10% [48/465]; P < .0001) compared with the placebo group. CONCLUSION: Pegfilgrastim was well tolerated and significantly decreased the incidence of FN, hospitalizations, and anti-infective use when used prophylactically. Commentary on Abstracts #8002, #620, and #A-52

**Jeffrey Crawford, MD** Given the magnitude of neutropenia and its consequences in the cancer chemotherapy patient, preventive strategies would certainly appear to be warranted. As mentioned in the introduction, for nearly a decade the ASCO guidelines have recommended that primary prophylaxis with colony-stimulating factors be restricted to patients who are at a 40% or greater risk for the development of febrile neutropenia. This was based on the control arms of the initial randomized clinical trials and was also supported by initial pharmacoeconomic data. More recent pharmacoeconomic data that take into account the rising cost of hospitalization and other expenses ([Lyman G, et al: Eur J Cancer 34[12]:1857-1864, 1998] have suggested that the risk threshold should be closer to 20% for the use of colony-stimulating factors to be relatively costneutral. 
However, this economic data preceded clinical trial data supporting the efficacy of colony-stimulating factors in this range, until the data from ASCO and MASCC of 2004. At ASCO, Timmer-Bonte and colleagues (ASCO abstract #8002) performed a prospective randomized-based study to evaluate the impact of filgrastim on patients with small-cell lung cancer receiving cyclophosphamide, doxorubicin, and etoposide, along with prophylactic antibiotics including ciprofloxacin and roxithromycin. For the group who received antibiotics alone, the incidence of febrile neutropenia was 23% in the first cycle and 30% in overall cycles. For the group receiving G-CSF, the incidence of febrile neutropenia was 10% in the first cycle and 18% overall, both statistically significant. While the absolute numbers for mortality from febrile neutropenia were low, the trend was in the same direction, with 7% of patients on the antibiotic arm dying compared to 3% of patients on the antibiotic plus G-CSF arm. A second study performed by the Spanish breast cancer research group, reported by Martin and colleagues (ASCO abstract #620), looked at prophylactic growth factor support in patients receiving adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC). In this study of women with node-positive breast cancer, the incidence of febrile neutropenia was high with the TAC regimen prompting an amendment in this study to include prophylactic G-CSF. The rates of febrile neutropenia were 23.8% prior to the institution of G-CSF and 3.5% for the patients enrolled in the subsequent part of the study. While there are limitations from this nonrandomized comparison, this magnitude of difference strongly suggests that G-CSF was effective in reducing the risk of febrile neutropenia with this regimen. The most convincing study was reported by Schwartzberg at MASCC (abstract #A52). In this trial, more than 950 breast cancer patients were enrolled in a prospective, double-blind placebo-controlled trial evaluating the impact of a single dose of pegfilgrastim 24 hours after docetaxel at 100 mg/m². This regimen was specifically chosen to try to assess the potential benefits of growth factor support in the setting associated with approximately 20% risk of febrile neutropenia. The results were striking. The placebo-control group experienced a 17% incidence of febrile neutropenia compared to a 1% incidence in the pegfilgrastim group. This corresponded with reduction in hospitalization from 14% to 1%, and reduction in intravenous antibiotic use from 10% to 2% in favor of the pegfilgrastim group. The results of these three trials are strikingly consistent and suggest a benefit at least as great as or greater than the previous clinical trials that evaluated G-CSF in treatment settings where the risk of febrile neutropenia was higher. In view of these benefits, it is anticipated that the guidelines committee of ASCO and NCCN will reevaluate the paradigm for treatment recommendations for primary prophylaxis with colony-stimulating factors in the cancer chemotherapy patient. As we define the patient at risk not only by the disease and chemotherapy regimen, we must also define individual factors that may place a patient at risk of febrile neutropenia. The appropriate interventions can then be made to reduce the current magnitude of and consequences from chemotherapy-induced neutropenia. **Understanding the Duration of Therapy** Abstract #A-50

A Meta-Analysis of Filgrastim Dosing Duration for the Treatment of Neutropenia From Standard and Dose-Intensified Chemotherapy

G. D. Demetri, Y. Mun, B. McGuire, R. D. Baynes

Dana-Farber Cancer Institute, Boston, Massachusetts; Amgen Inc, Thousand Oaks, California

A meta-analysis was conducted to study the average number of days of filgrastim dosing within a cycle that were needed to achieve neutrophil (ANC) recovery following myelosuppressive chemotherapy. Aggregate statistics from 10 phase I or phase II studies were used (see Table 1). Each study treated a specific solid or lymphoid tumor with conventional chemotherapy regimens, first at standard doses and then at incrementally intensified doses using dose escalation and/or shortened cycle lengths.
Filgrastim was dosed at 5 or 10 μg/kg/d starting after chemotherapy and through two ANC observations ≥ 10 * 10^9 L. Data were available from 334 patients: 138 who received standard chemotherapy doses and 196 who received escalated chemotherapy. Total days of filgrastim administered in cycle 1 were analyzed using a random effects meta-analysis model. For cohorts receiving standard chemotherapy (including shortened cycles), the pooled mean days of filgrastim was 12.4 days (95% CI = 9.8-15.0 days). Individual study means ranged from 2.5 to 17.0 days. The lowest mean value (2.5) represented a study using a nitrosourea; which is known to elicit mild and delayed neutropenia. In patients receiving escalated doses of chemotherapy, the pooled mean of filgrastim dosing duration in cycle 1 was 15.6 days (95% CI = 13.7-17.4 days). At high doses of chemotherapy, delayed initiation of filgrastim or premature discontinuation was associated with prolonged neutropenia (or failure to achieve a sustained ANC recovery) and subsequent cycle delays. CONCLUSION: This analysis demonstrated that in the setting of standard doses of chemotherapy, approximately 12 days per cycle of filgrastim were required to achieve this level of ANC recovery. When chemotherapy was escalated, longer durations of dosing were required. Initiating filgrastim dosing too late in the cycle and/or stopping too soon were found to be deleterious to achieving a stable ANC for delivery of the next cycle of chemotherapy. Abstract #A-59

**Duration of G-CSF Prophylaxis and Risk of Hospitalization Among Patients With Non-Hodgkin's Lymphoma, Breast Cancer, and Lung Cancer**

D. Weycker, J. Hackett, J. Edelsberg, G. Oster, A. Glass
Policy Analysis Inc, Brookline, Massachusetts; Amgen Inc, Thousand Oaks, California; Kaiser Permanente Northwest, Portland, Oregon

In clinical trials, granulocyte colony-stimulating factor (G-CSF) prophylaxis, when administered for an average of 10 to 11 days, has been found to reduce the incidence of febrile neutropenia in patients receiving myelosuppressive chemotherapy. In clinical practice, however, many patients receive shorter courses of prophylaxis. The effectiveness of these shorter courses is unknown. Using a large US health-care claims database, we identified all adults with non-Hodgkin’s lymphoma (NHL), breast cancer (BC), or lung cancer (LC) who received myelosuppressive chemotherapy between 1998 and 2002. For these persons, we further identified their first such course of chemotherapy and each unique cycle within that course. We then focused attention on all patient-cycles in which G-CSF was administered on or before cycle day 5 (“G-CSF prophylaxis”). Pooling all such cycles, we used a Generalized Estimating Equation (GEE) model (with a logistic link function) to examine the relationship between duration of G-CSF prophylaxis and risk of hospitalization for neutropenia or infection and risk of hospitalization for any reason, controlling for potential confounders. Mean (SD) duration of G-CSF prophylaxis was 6.5 (3.1) days across 332 patient-cycles in those with NHL, 6.1 (2.9) days across 482 patient-cycles in those with BC, and 4.3 (3.1) days across 522 patient-cycles in those with LC. There were 29 cycles with a hospitalization for neutropenia or infection among NHL...
patients, 21 among BC patients, and 45 among LC patients. The predicted risk of hospitalization for neutropenia or infection declined with each additional day of G-CSF prophylaxis for patients with NHL (odds ratio [OR] = 0.81; \( P = .003 \)), BC (OR = 0.78; \( P = .002 \)), and LC (OR = 0.92; \( P = .119 \)) (see Table 1). Results were similar for analyses of hospitalization for any reason.

**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NHL</th>
<th>Breast Cancer</th>
<th>Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>( P ) value</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Number of G-CSF days</td>
<td>0.81</td>
<td>.003</td>
<td>0.78</td>
</tr>
<tr>
<td>Cycle 1 (vs cycles 2–9)</td>
<td>1.62</td>
<td>.299</td>
<td>4.22</td>
</tr>
<tr>
<td>Prior hospitalization for neutropenia/infection</td>
<td>1.46</td>
<td>.633</td>
<td>2.48</td>
</tr>
<tr>
<td>Presence of anemia</td>
<td>2.08</td>
<td>.098</td>
<td>1.49</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>1.28</td>
<td>.009</td>
<td>1.11</td>
</tr>
</tbody>
</table>

CONCLUSION: Among patients with NHL, BC, and LC receiving G-CSF prophylaxis, longer courses of therapy confer lower risks of hospitalization. **Commentary on Abstracts #A-50 and #A-59**

**Jeffrey Crawford, MD** At MASCC, two studies evaluated the impact of the duration of filgrastim dosing on the risk of development of neutropenia and its consequences. In the report from Demetri and colleagues (abstract #A-50), a meta-analysis was performed that demonstrated that in the setting of standard dose chemotherapy, approximately 12 days per cycle of filgrastim was required to achieve adequate ANC recovery. With escalated doses of chemotherapy even longer durations of dosing were required. Initiating G-CSF too late in the cycle or stopping too soon were also found to be less beneficial in achieving stable ANC. In abstract #A-59, Weycker and colleagues report results of G-CSF prophylaxis using a large US health-care claims database. Interestingly, in this very different data set, the results were similar to the meta-analysis of clinical trials reported by Demetri. That is, among patients with non-Hodgkin's lymphoma, breast cancer, and lung cancer who received G-CSF prophylaxis, longer courses of therapy confer lower risks of hospitalization. These results are quite important to help validate the necessity of prolonged use of G-CSF with myelosuppressive chemotherapy regimens to reduce the risk of neutropenia. Since the registrational trials for pegfilgrastim included a control arm of filgrastim use of 11 days, this also validates the appropriateness of current pegfilgrastim dosing in order to achieve full benefits of either agent in the setting of myelosuppressive chemotherapy. **Neutropenia and Lung Cancer Abstract #7223**

**Risk and Mortality Associated With Febrile Neutropenia in Lung Cancer Patients** D. B. Daniel, J. Crawford, N. M. Kuderer, D. C. Dale, G. H. Lyman, for the ANC Study Group Duke University Medical Center, Durham, North Carolina; University of Rochester Medical Center, Rochester, New York; University of Washington Medical Center, Seattle, Washington Myelosuppression and its complications represent the major dose-limiting toxicities of lung cancer chemotherapy. Length of stay (LOS), mortality, and cost associated with febrile neutropenia were studied in 3,340 lung cancer patients experiencing 3,846 admissions to 115 academic institutions reporting to the University HealthSystem Consortium between 1995 and 2000. Those factors found to be significantly associated with complicated hospitalizations (length of stay \( \geq 8 \) days) or inpatient mortality were evaluated in logistic regression models. Estimates of relative risk associated with each risk factor.
were based on the adjusted odds ratios (OR ± 95% CIs) for mortality and LOS greater than 8 days. Overall inpatient mortality was 12.1%. Factors significantly associated with increases in the risk of inpatient mortality included metastases (OR 2.28 [95% CI = 1.81-2.88]), hypotension (OR 3.79 [95% CI = 2.55-5.62]), pneumonia (OR 2.39 [95% CI = 1.90-3.01]), and gram-negative bacteremia (OR age ≥ 65: 8.13; OR age ≤ 65: 3.75). The mean and median LOS were 8.1 and 5 days, respectively. The mean LOS was 8.1 days, median 5 days. Hospital LOS was ≥ 8 days in 32.4% patients. Factors significantly associated with longer LOS included congestive heart failure (OR 2.18 [95% CI = 1.61-2.94]), functional impairment (OR 1.98 [95% CI = 1.35-2.90]), pneumonia (OR 1.94 [95% CI = 1.63-2.31]), and gram-positive bacteremia (OR 3.42 [95% CI = 2.30-5.11]). Patients whose primary reason for admission was other than febrile neutropenia had higher risk of mortality (OR 3.40 [95% CI = 2.49-4.64]) and LOS ≥ 8 days (OR 3.18 [95% CI = 2.68-3.77]). Model R2 for the mortality and LOS models were 0.126 and 0.123, respectively, while the c-statistics (ROC AUC) were .790 and .718.

CONCLUSION: Mortality in lung cancer patients hospitalized for febrile neutropenia is greater than for other solid tumors. Increasing age, advanced disease, nutritional and functional impairments, and comorbidities along with infectious complications lead to prolonged hospitalization and increased risk of mortality. Prospective studies are warranted to further define risk factors and evaluate possible interventions.

**Japan-SWOG Common Arm Analysis of Paclitaxel/Carboplatin in Advanced Stage Non-Small-Cell Lung Cancer: A Model for Prospective Comparison of Cooperative Group Trials**

D. R. Gandara, Y. Ohe, K. Kubota, Y. Nishiwaki, Y. Ariyoshi, N. Saltjo, S. Williamson, P. N. Lara, J. Crowley, M. Fukuoka University of California Davis Cancer Center, Sacramento, California; FACS Cooperative Group, Tokyo, Japan; University of Kansas, Kansas City, Kansas; Southwest Oncology Group, San Antonio, Texas

Whether results of clinical trials performed outside the United States can be fully extrapolated to US populations remains in question due to potential differences in trial designs, study-specific criteria, patient demographics, and population-related pharmacogenomics. We prospectively designed and conducted separate phase III trials in advanced non-small-cell lung cancer (NSCLC) linked by a "common arm" with identical eligibility, staging, response, and toxicity criteria, to (1) determine similarities and differences in patient demographics and outcomes in cooperative group trials in Japan (Four-Arm Cooperative Study or FACS) and the United States (SWOG 0003), (2) provide the basis for global standardization in clinical trials in NSCLC, and (3) facilitate regulatory changes needed for joint Japan-US studies sponsored by the US National Cancer Institute (NCI). We performed a planned comparative analysis of the paclitaxel/carboplatin arms from FACS and S0003, identical except for paclitaxel dose of 200 mg/m² in FACS and 225 mg/m² in S0003, based on the MTD from separate phase I studies in Japan and the US. Carboplatin AUC 6 was used in
both. See Table 1:

<table>
<thead>
<tr>
<th>Selected Parameters</th>
<th>FACS</th>
<th>S0003</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>145</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>Age (median)</td>
<td>63 yr (33–74 yr)</td>
<td>63 yr (28–80 yr)</td>
<td>.34</td>
</tr>
<tr>
<td>Females</td>
<td>46 (32%)</td>
<td>68 (37%)</td>
<td>.12</td>
</tr>
<tr>
<td>Stage IV</td>
<td>117 (81%)</td>
<td>161 (87%)</td>
<td>.32</td>
</tr>
<tr>
<td>Histology (nonsquamous)</td>
<td>125 (79%)</td>
<td>152 (82%)</td>
<td>.32</td>
</tr>
<tr>
<td>Weight loss &gt; 5%</td>
<td>NA</td>
<td>57 (31%)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia (grade 4)</td>
<td>102 (69%)</td>
<td>48 (26%)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Febrile neutropenia (grade 3/4)</td>
<td>24 (16%)</td>
<td>6 (3%)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Neuropathy (grade 3/4)</td>
<td>7 (5%)</td>
<td>30 (16%)</td>
<td>.001</td>
</tr>
<tr>
<td>Median cycles delivered</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Response (CR + PR)</td>
<td>47 (32%)</td>
<td>63 (34%)</td>
<td>.75</td>
</tr>
<tr>
<td>MST</td>
<td>12 mo</td>
<td>9 mo</td>
<td></td>
</tr>
<tr>
<td>1-yr survival</td>
<td>51%</td>
<td>37%</td>
<td>.009</td>
</tr>
</tbody>
</table>

CONCLUSION: (1) This common arm analysis shows great similarities in patient demographics between FACS and S0003. (2) Variable toxicities may be due to differences in cumulative paclitaxel dose (neuropathy) and/or population-related pharmacogenomics (increased neutropenia and febrile neutropenia in FACS despite lower paclitaxel dose). (3) Survival is increased in FACS. (4) Future joint Japan-US clinical trials should consider possible pharmacogenomic differences in drug disposition. Abstract #7041

**Influence of Gender on Treatment Outcome and Toxicity in Small-Cell Lung Cancer**

Singh, W. Parulekar, N. Murray, R. Feld, B. Evans, D. Tu, J. Pater, F. A. Shepherd Princess Margaret Hospital, Toronto, Ontario, Canada; National Cancer Institute of Canada, Kingston, Ontario, Canada; British Columbia Cancer Agency, Vancouver, British Columbia, Canada; Cancer Care Ontario, Toronto, Ontario, Canada. Female gender has been shown consistently to be a favorable prognostic factor in small-cell lung cancer (SCLC). Studies have shown that women with other tumor types experience greater treatment toxicity, but there have been few studies of gender-related toxicity in SCLC. This was a gender-based retrospective analysis of four SCLC trials that were conducted by the NCIC CTG between 1981 and 1996. All 1,006 patients (648 male, 358 female) received similar chemotherapy consisting of cyclophosphamide/doxorubicin/vincristine and etoposide/cisplatin. Toxicities examined included myelosuppression, stomatitis, vomiting, and infection. Other end points included number of dose reductions required, number of omitted cycles, response rates, and overall survival. Toxicities between the genders were compared using the chi-square test in univariate analyses and logistic regression adjusting for age, BSA, performance status, lactate dehydrogenase, and individual trial in multivariate analyses. Women experienced significantly more toxicity in both univariate and multivariate analyses (see table). However, toxic death rates were similar for men and women (1.5% vs 1.1%, P = .58). Despite increased toxicity, 76% of females vs 73.4% of males received all six treatment cycles (P = .38), but 52% of females vs 43.4% of males had treatment.
delayed for ≥ 2 weeks (P = .022). The ORR was 80.3% for females and 66.9% for males (P < .0001) and the median survival was 1.31 years for females and 0.91 for males (P < .0001). CONCLUSION: Women clearly experience more chemotherapy-related toxicity in the treatment of SCLC, but this does not result in more toxic deaths or omitted treatment cycles, nor does it compromise outcome.

See Table 1 below.

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>All Grades</td>
<td>Grade 3/4</td>
<td>All Grades</td>
</tr>
<tr>
<td></td>
<td>55.9%</td>
<td>16.3%</td>
<td>38.6%</td>
</tr>
<tr>
<td>Platelets</td>
<td>37.4%</td>
<td>10.9%</td>
<td>35.7%</td>
</tr>
<tr>
<td>WBC</td>
<td>92.7</td>
<td>80.4</td>
<td>64.7</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>16.8%</td>
<td>3.1%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>76.8%</td>
<td>19.3%</td>
<td>67.2%</td>
</tr>
<tr>
<td>Infection</td>
<td>43.5%</td>
<td>4.5%</td>
<td>14.2%</td>
</tr>
</tbody>
</table>

Hgb = hemoglobin; WBC = white blood cells.

**A Phase II Study of Pegfilgrastim to Support ACE 14 Chemotherapy for the Treatment of Subjects With Small-Cell Lung Cancer**

R. Pirker, E. Ulspenger, K. Aigner, J. Messner
Vienna Medical University, Vienna, Austria; Krankenhaus Lainz, Vienna, Austria; Krankenhaus der Elisabethinen, Linz, Austria; Landesklinik für Lungenkrankheiten, Salzburg, Austria

Thatcher et al (J Clin Oncol 18:395-404, 2000) showed that dose-dense ACE (doxorubicin [Adriamycin], cyclophosphamide, etoposide) with G-CSF allows delivery of "chemotherapy planned dose on time" (CPDOT), leading to improved survival in subjects with extensive small-cell lung cancer (SCLC). The aim of this study was to show that pegfilgrastim can also support ACE 14 CPDOT in this setting. All 30 subjects received ACE (doxorubicin 40 mg/m² and cyclophosphamide 1,000 mg/m² IV day 1, etoposide 120 mg/m² IV day 1 and 240 mg/m² po days 2 and 3) every 14 days for up to 6 cycles, with a single dose per cycle of pegfilgrastim 6 mg SC on day 4. A cycle was considered "on time" if it started no more than 17 days after the start of the previous cycle, and "at planned dose" if 75% of drug was administered for each agent. For any given cycle, subjects were defined as having CPDOT if both criteria were satisfied. Twenty-seven subjects received pegfilgrastim and at least 1 cycle of ACE and 17 received all 6 cycles of ACE. Twenty subjects (74%) had no bone marrow involvement at baseline. The mean baseline ANC was 7.4 * 10⁹/L (range: 3.0-23.3); over the study, mean ANC levels at the start of each cycle were 1.5 * 10⁹/L and were comparable to baseline levels. All 22 subjects who started cycle 2 received full CPDOT. Of the 121 cycles delivered over the study, 107 (88%) were full CPDOT. In addition, 18 subjects (67%) received all their cycles according to full CPDOT. Of the 22 subjects who were assessed for disease response, 2 (9%) had complete response, 15 (68%) partial response (with an overall response rate of 77%), and 2 (9%) stable disease. Safety data were consistent with the underlying patient group. Nine (33%) and 6 (22%) subjects experienced hematologic and nonhematologic events of toxicity grade 3/4: anemia 15%, leukopenia 7%, thrombocytopenia 11%, and febrile neutropenia 15%. All other adverse events were single episodes. CONCLUSION: These results indicate that pegfilgrastim enables delivery of dose-intensified ACE chemotherapy every 14 days in SCLC patients.

**Prospective Multicenter Phase II Trial of Docetaxel and Vinorelbine With Filgrastim Support in Subjects With Advanced Non-Small-Cell Lung Cancer**

Texas Cancer Care, Weatherford, Texas; Sibley Memorial Hospital, Washington, DC; Charleston Hematology/Oncology, Charleston, South Carolina; Morgantown Internal Medicine/Oncology, Morgantown, West Virginia; AMF Consulting, Los Angeles, California; Amgen, Inc, Thousand Oaks, California

Although platinum-based chemotherapy (CT) regimens are the standard of therapy in first-line non-small-cell lung cancer (NSCLC), a subset of patients are ineligible to receive such agents. Docetaxel and vinorelbine are each active agents in NSCLC, and when combined may provide enhanced activity. The purpose of this study was to evaluate the safety and efficacy of this combination therapy when administered on a every-2-week schedule with filgrastim support. This multicenter, community-based study was conducted in 10 sites that enrolled 61 CT-naive patients with stage IIIIB/IV NSCLC. Treatment consisted of vinorelbine 45
mg/m² and docetaxel 60 mg/m² day 1 and filgrastim 5 μg/kg days 2-14 repeated every 2 weeks for 8 cycles. Patients were evaluated for response at the end of cycles 2, 5, and 8. Confirmed response was defined as complete or partial response based upon two or more evaluations, while best response was defined as the best of the three evaluations. We report response rate and Kaplan-Meier estimate (95%CI) of time to disease progression and 1-year survival. Of 61 enrolled patients 42% (95% confidence interval [CI] = 30%-54%) achieved either complete response or partial response as best response; 13% (95% CI = 9%-17%) of patients had a confirmed response. Median time to disease progression was 160 days. With a median follow-up time of 14.2 months, the estimated median survival time is 14.1 months (95% CI lower bound, 8.5 mo), and the 1-year survival rate is 57% (95% CI = 44%-70%). Five patients (8%) experienced febrile neutropenia (ANC < 500/mm³ plus body temperature ≥ 38.2°C). Overall calculated dose intensity (delivered/planned dose * 100) was 95% for vinorelbine and 93% for docetaxel. CONCLUSION: The combination of docetaxel and vinorelbine can be delivered with high dose intensity with filgrastim support. Additionally in this multicenter noncontrolled study completed in a community setting, an interesting 1-year and overall median survival is observed and supports further evaluation. Commentary on Abstracts #7223, #7007, #7041, #7216, and #7138

Jeffrey Crawford, MD Extending the observations from the UHC database previously discussed, Daniel and colleagues (ASCO abstract #7223) reviewed the risk and mortality associated with febrile neutropenia in lung cancer patients. What was striking from their results was that the overall inpatient mortality was quite distinct from other solid tumor patients and approached that of patients with hematologic malignancies, with an overall inpatient mortality of 12.1%. Factors associated with risk of inpatient mortality included metastatic disease, hypotension, pneumonia, and gram-negative bacteremia. Increasing age, advanced disease, nutritional and functional impairments, and comorbidities, along with these infectious complications, led to both risk of prolonged hospitalization and increased risk of mortality. Based on these data, prospective studies are warranted to evaluate strategies to reduce the risk of febrile neutropenia in the high-risk setting of lung cancer. To further refine patients at risk, Gandara et al (ASCO abstract 7007) compared a carbo-platin/paclitaxel regimen from the results of a Japanese study (FACS) and SWOG S0003. Both studies used a carboplatin dose of AUC 6, with a paclitaxel dose of 200 mg/m² in FACS and 225 mg/m² in S0003. Despite the slightly lower paclitaxel dose, the incidence of neutropenia occurred in 69% of the Japanese population vs 26% of the North American population. The febrile neutropenia rate was 16% in the Japanese population and 3% in the North American population. This variable toxicity suggests the potential for population-related pharmacogenomic differences and requires further study. In a retrospective review of four small-cell lung cancer trials from the NCIC group, Singh and colleagues (ASCO abstract #7041) demonstrated that women clearly experienced more chemotherapy-related toxicity in the treatment of small-cell lung cancer than men. Women were significantly more likely to develop grade 3 or 4 leukopenia and also experienced more anemia, stomatitis, and vomiting. In addition to increased toxicity, the overall response rate and mean survival was also greater for women compared with men. These gender differences are striking, and again provide clues to optimized chemotherapy dosing while preemptively managing treatment toxicities in populations at higher risk. In this regard, two studies reported the potential for growth factor support to facilitate the use of dose dense chemotherapy. Pirker and colleagues (ASCO abstract #7216) reported the results of the phase II study of pegfilgrastim to support ACE 14-day chemotherapy for the treatment of patients with small-cell lung cancer. Two thirds of the patients received all their cycles of chemotherapy at full dose on time, demonstrating the ability to deliver a dose-dense myelosuppressive regimen every 2 weeks. The treatment outcomes were encouraging. This strategy of dose-dense therapy may have application for further study in earlier stages, not only in small-cell lung cancer but perhaps in non-small-cell lung cancer as well. In that regard, Page and colleagues (ASCO abstract #7138) reported the results of a multicenter phase II trial of docetaxel and vinorelbine with filgrastim support. Again the results were encouraging in the setting of advanced-stage non-small-cell lung cancer. Evaluations of these strategies in earlier stages of the disease may provide more definitive results of potential benefit. Neutropenia and Breast Cancer Abstract #A-36

Predicting Neutropenic Risk and Reduced Chemotherapy Dose Intensity in Patients With Early-Stage Breast Cancer: Results From a Prospective Nationwide Registry G. H. Lyman, J. Crawford, D. Wolff, E. Culakova, M. Poniewierski, D. C. Dale, for the ANC Study Group University of Rochester, Rochester, New York; Duke University, Durham, North Carolina; University of Washington, Seattle, Washington Chemotherapy-induced neutropenia is frequently associated with neutropenic
complications (NC) resulting in reduced relative dose intensity (RDI), potentially compromising patient outcomes. Retrospective analyses have identified several risk factors for NC and reduced RDI, but these studies are limited by variable reporting and missing data. To overcome these limitations, a prospective registry of patients with breast cancer at 137 centers has been established. More than 2,500 patients initiating a new chemotherapy regimen have been registered, including 617 patients with early-stage breast cancer-525 of whom have completed at least one cycle of chemotherapy. Primary outcomes include ANC < 1,000 (58%), neutropenic complications (ANC < 500 or infection) (42%), and RDI < 85%. Regimens include AC or ACT (53%), CMF (12%), and CAF (9%). Both unconditional (pretreatment) and conditional (based on first cycle event) models for risk of NC and reduced RDI have been developed. In unconditional models, significant predictors of NC include anthracycline regimens (OR = 7.9) and prior chemotherapy (OR = 3.52) (model \( P < .001; R^2 = 0.15; \) c-statistic 0.62). In conditional models, significant predictors of NC include first cycle ANC nadir (OR = 8.98), first cycle infection (OR = 3.15), prior chemotherapy (OR = 10.02); and BSA > 2 m\(^2\) (OR = 0.51) (model \( P < .001; R^2 = 0.61; \) c-statistic 0.86). In models for reduced RDI, stage of disease and practice center were also significant independent predictors. CONCLUSION: Recent large practice pattern surveys have shown that breast cancer patients often receive reduced chemotherapy dose intensity, primarily due to NC. A reliable tool to identify patients at risk for NC should permit more rational use of targeted supportive care and delivery of improved chemotherapy dose intensity. Abstract #776

**Predicting the Risk of Neutropenic Complications and Reduced Dose Intensity in Patients With Early-Stage Breast Cancer: Results From a Prospective Nationwide Registry**

G. H. Lyman, J. Crawford, D. C. Dale, D. A. Wolff, E. Culakova, for the ANC Study Group University of Rochester Medical Center, Rochester, New York; Duke University Medical Center, Durham, North Carolina; University of Washington Medical Center, Seattle, Washington Chemotherapy-induced neutropenia is frequently associated with neutropenic complications resulting in reduced relative dose intensity (RDI), potentially compromising patient outcomes. Retrospective analyses have identified several risk factors but are limited by variable reporting and missing data. A prospective registry of chemotherapy patients at 137 centers has been established. Both unconditional (pretreatment) models and models conditional on first-cycle events for risk of neutropenic complications and reduced RDI have been developed. Overall, 2,222 patients have been registered prior to chemotherapy, including 617 patients with early-stage breast cancer (ESBC), of which 525 have completed at least one cycle of chemotherapy. Adverse outcomes include ANC < 1,000 (58%), neutropenic complications (ANC < 500 or infection) (42%), and RDI < 85% (11.3%). Regimens include AC or AC-T (53%), CMF (12%), and CAF (9%). In unconditional models, significant predictors of neutropenic complications include anthracycline regimens (OR = 7.9) and prior chemotherapy (OR = 3.52) (model \( P < .001; R^2 = 0.15; \) c-statistic 0.62). In models conditional on first-cycle events, significant predictors of neutropenic complications include first cycle nadir (OR = 8.98), first-cycle infection (OR = 3.15), prior chemotherapy (OR = 10.02), and body surface area > 2 m\(^2\) (OR = 0.51) (model \( P < .001; R^2 = 0.61; \) c-statistic 0.86). In models for reduced RDI, stage and practice center were also significant independent predictors. Separate validation of these models will be presented. CONCLUSION: Recent large practice surveys demonstrate that breast cancer patients often receive reduced chemotherapy dose intensity, primarily due to neutropenic complications. A reliable tool to identify patients at risk for neutropenic complications should permit more rational use of targeted supportive care and delivery of optimal chemotherapy dose intensity. Abstract #677

**The Role of Growth Factor Support Following Neutropenic Events in Early-Stage Breast Cancer Patients Treated With Adjuvant Docetaxel, Doxorubicin, and Cyclophosphamide: A Subanalysis of BCIRG 001**

C. L. Vogel, J. R. Mackey, M. Martin, on behalf of the BCIRG 001 Investigators Cancer Research Network, Plantation, Florida; Cross Cancer Institute, Edmonton, Alberta, Canada; Hospital Universitario San Carlos, Madrid, Spain Docetaxel, doxorubicin, and cyclophosphamide (TAC) significantly improves disease-free and overall survival over FAC (hazard ratio 0.70 and 0.68, respectively), and is emerging as one of the most active adjuvant treatments in patients with node positive early-stage breast cancer (Martin M: SABCS 2003 abstract #43). TAC is generally well tolerated, but is associated with a higher incidence of febrile neutropenia (FN) vs FAC. ASCO Clinical Practice Guidelines recommend secondary prophylaxis with G-CSF after FN in a prior cycle to maintain dose intensity. Patients with node-positive breast cancer were randomized to TAC (75/50/500 mg/m\(^2\) q3wk *6) or FAC (500/50/500 mg/m\(^2\) q3wk *6). Corticosteroid premedication and prophylactic ciprofloxacin were given with TAC, but not with FAC. In case of FN (grade 2 fever with grade 4 neutropenia), patients were treated with G-CSF for all subsequent cycles. This retrospective subgroup analysis compares the incidence of FN for cycles treated without and with G-CSF. A total of
1,491 patients were accrued, with 1,480 evaluable for safety (TAC 744, FAC 736). A similar number of cycles were delivered in both arms (TAC 4010, FAC 4007). Febrile neutropenia occurred as follows: TAC, 183 patients (24.7% patients, 5.4% cycles); FAC 18 patients (2.5% pts, 0.5% cycles), with at least half the FN occurring in the first cycle (TAC: 97/183 patients, FAC 9/18 patients). G-CSF was administered to 250 TAC patients and 93 FAC patients. Among these, G-CSF was used as secondary prophylaxis for 87% (TAC) and 44% (FAC) of patients. The rate of FN (per cycle) without vs with G-CSF among all patients was as follows: TAC 187/3,114 (6.0%) vs TAC+G-CSF 28/896 (3.1%); FAC 19/3,704 (0.5%) vs FAC+G-CSF 1/303 (0.3%). There were no septic deaths during treatment with either TAC or FAC, regardless of the use of GCSF. CONCLUSION: Among patients treated with TAC, the use of G-CSF decreased the incidence of neutropenic complications, although it remained higher than for pts treated with FAC. For patients experiencing a neutropenic event with TAC, secondary prophylaxis with G-CSF is appropriate. The impact of G-CSF on other clinical safety parameters will also be presented. Abstract #619

**Dose-Limiting Effects of Neutropenic Events in Six European Audits of Adjuvant Breast Cancer Chemotherapy**

R. Leonard, T. D. Szucs, R. Pettengell, R. Paridaens, C. Jackisch, M. Constenla, A. Bosly, M. Schwenkglenks, for the Impact of Neutropenia in Chemotherapy European Study Group (INC-EU) South West Wales Cancer Institute, Swansea, United Kingdom; European Center of Pharmaceutical Medicine, Basel, Switzerland; St George's Hospital, London, United Kingdom; University Hospital Gasthuisberg, Leuven, Belgium; University Hospital Marburg, Marburg, Germany; Complexo Hospitalario de Pontevedra, Pontevedra, Spain; Cliniques Universitaires UCL, Godinne, Belgium Retrospective audits of adjuvant breast cancer chemotherapy (CT) were performed in several European countries. Results of a combined analysis of six audits from Austria, Belgium, Germany, Spain, and the United Kingdom are reported. Variables available in all six datasets were merged into a dataset of individual observations and their definitions were harmonized. We assessed the incidence of neutropenic events and of low average relative CT dose intensity (ARDI). Adjusted odds ratios (ORs) of low ARDI occurrence were calculated by robust multiple logistic regression. Neutropenic events were defined as neutropenia-related hospitalization, dose reduction ≥ 15%, and/or dose delay ≥ 7 days. Low ARDI was defined as ARDI ≤ 85%. A total of 2,633 patients had a mean age at diagnosis ± standard deviation of 51.0 ± 11.3 years (interaudit range [IAR]: 48.0 ± 10.9 to 52.5 ± 11.7 years). Patients were postmenopausal in 51% of cases and 64% were hormone receptor positive. The diagnostic spread was stage I 19%, II 65%, and III 16%. Fiftyeight percent received CMF-based regimens, 39% anthracycline-containing, and 3% other regimens. Concomitant radiotherapy was reported in 32%, and use of colony-stimulating factors (CSF) in 12%. In 3%, CSF use started in cycle 1. Neutropenic events were observed in 20% of patients (IAR: 14%-27%). Repeated neutropenic events were seen in 8% (IAR 6%-11%). Low ARDI was observed in 14%. In those without and with neutropenic events, low ARDI was observed in 6% vs 17% (P < .005). Low ARDI was independently associated with neutropenic event occurrence (OR 4.9, 95% CI 3.6-6.7); use of a nonanthracycline regimen (OR 1.5, 95% CI = 1.1-1.9); concomitant radiotherapy (OR 1.3, 95% CI = 1.1-1.5); and disease stage. Odds ratios for stages II and III, compared to stage I, were 1.5 (95% CI = 1.2-2.0) and 1.6 (95% CI = 1.2-2.3). A more restrictive neutropenic event definition based on the cell count data available lead to an OR of 2.6 (95% CI = 1.7-3.7) for low ARDI, with the other coefficients stable. CONCLUSION: Neutropenic events occurred in a relevant proportion of patients receiving breast cancer CT and showed a robust association with low ARDI, which may affect treatment outcomes. Ongoing prospective research should address the development of risk models to target preventive measures and optimize CT. Abstract #583

**Reducing Dose Density in Adjuvant Chemotherapy Is Detrimental in Early Breast Cancer: A Review of 872 Adjuvant Treatments in Centre Francois Baclesse**

T. Delozier, C. Sgura, C. Levy, C. Delcambre, D. Allouache, O. Switsers, J.-M. Ollivier, B. Vi, F. Joly, J.-Y. Gnot Centre Francois Baclesse, Caen, France Dose density is a key in the efficacy of chemotherapy. This concept has been tested in increasing dose density, especially in the adjuvant setting. Side effects of chemotherapy such as leukopenia can induce delay in dose administration, leading to a decrease in dose density. The aim of the study was to evaluate the impact of reducing dose density in adjuvant chemotherapy in early breast cancer. We compared disease-free survival and overall survival according to dose density expressed in treatment duration for women treated with the same chemotherapy in our institution. We reviewed data from 872 women who received six cycles of chemotherapy using the FEC60 regimen (5-FU 600 mg/m², epirubicin 60 mg/m², cyclophosphamide 600 mg/m²) on day 1 repeated every 3 weeks. All estrogen receptor positive (ER+) patients received adjuvant tamoxifen for 5 years. According to the protocol, chemotherapy administration was postponed for 1 week if patients presented leukopenia on day 1. No reduction in the applied dose was performed. Overall,
181 patients (group 1) underwent their six cycles of chemotherapy without any delay. In 343 patients (group 2), chemotherapy was delayed up to three times: treatment duration between 110 and 130 days. Chemotherapy was delayed more than three times in 350 patients (group 3): treatment duration greater than 130 days. The distribution of main characteristics was similar in the groups. The median duration of treatment was 125 days (range: 100-195 days). Median age was 47 years (range: 25-69 years), 66% were premenopausal, 63% node positive, 66% ER positive. The median follow-up is 4 years. Overall, 35, 75, and 117 patients relapsed in the three groups, respectively, leading to a 4-year disease-free survival (DFS) rate of 79.4%, 76.0%, and 66.1% respectively (P = 0.09). Patients who underwent chemotherapy in more than 130 days had a higher risk of relapse (P = 0.03). No difference was observed in overall survival. CONCLUSION: We conclude that although no survival disadvantage is noted, the not respecting time schedules in chemotherapy is detrimental in early breast cancer patients. Abstract #552

Impact of Reduced Dose Intensity of Adjuvant Anthracycline-Based Chemotherapy in a Population-Based Cohort of Stage I/II Breast Cancers

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Reductions in the dose intensity of adjuvant doxorubicin and cyclophosphamide (AC) chemotherapy in the treatment of early-stage breast cancer are frequently required, with the impact on clinical outcome uncertain. We examined whether a reduced dose intensity had an impact on relapse-free survival (RFS), breast cancer-specific survival (BCSS), or overall survival (OS) in a population-based cohort of early-stage breast cancers treated with adjuvant AC. Women with stage I/II breast cancer treated with adjuvant AC (A: 60 mg/m², C: 600 mg/m² on a 21-day schedule) between 1990 and 1995 were retrospectively identified through the British Columbia Cancer Agency (BCCA) pharmacy database and linked to the BCCA Breast Cancer Outcomes Unit database. A dose reduction was defined as a reduction of at least one of the chemotherapy agents by at least 25% in any given cycle. Dose delay was defined as a delay in delivering treatment by at least 5 days. Cases were classified into the following four cohorts: cohort 1, entire course of treatment delivered at full doses and on time; cohort 2, one single dose reduction or dose delay; cohort 3, more than one dose reduction or dose delay; cohort 4 = two cycles of chemotherapy delivered. No growth factor support was utilized in any cases. A total of 484 cases were retrospectively identified (cohort 1, n = 268; cohort 2, n = 88; cohort 3, n = 89; cohort 4, n = 39) with a median follow-up of 9.6 years. The four cohorts were well matched for most baseline prognostic factors except for slight imbalances in lymph node status (P = .05) and adjuvant hormonal therapy (P = .05). Fifty-five percent of the entire cohort had node-positive disease. Overall 45% of cases had a reduced dose intensity delivered. However, there were no significant differences in 8 year RFS (P = .94), BCSS (P = .87), and OS (P = .86) between the four cohorts. The 8-year outcomes for cohorts 1 through 4, respectively, were RFS (72%, 74%, 74%, 68%), BCSS (80%, 77%, 82%, 80%), and OS (78%, 76%, 80%, 77%). CONCLUSION: Although reductions in the dose intensity of adjuvant AC chemotherapy for early-stage breast cancer was common, it did not appear to significantly impact on clinical outcomes in this cohort of patients with stage I/II breast cancer. Abstract #589

A Phase III Randomized Trial Comparing the Tolerability of Dose-Dense Chemotherapy in Older to That in Younger Breast Cancer Patients With Four or More Positive Lymph Nodes


Department of Senology, Campus Charit Mitte, Berlin, Germany; Krankenhaus Lichtenberg, Berlin, Germany; Stdt. Krankenhaus Ludwigsfelde, Germany; Humaine-Klinikum, Bad Saarow, Germany; Stdt. Krankenhaus, Neunkirchen, Germany; Stdt. Klinikum, Stralsund, Germany; Stdt. Klinikum, Leipzig, Germany

Recently published data showed older patients to have similar dose-related benefits in reducing breast cancer-related relapse and mortality to those of younger women. This analysis was performed to assess the feasibility of a prospective randomized dose-dense regimen in the treatment of women over the age of 60. From June 1996 to November 2000, 211 primary breast cancer patients with four or more positive lymph nodes were prospectively randomized to either four cycles of epirubicin and paclitaxel (ET) at 2-week intervals followed by three cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF) with G-CSF support (group A) (age < 60 years [A1], n = 79; age ≥ 60 years [A2], n = 25), or four cycles of epirubicin and cyclophosphamide (EC) at 3-week intervals followed by three cycles of CMF (group B) (age < 60 years [B1], n = 80; age ≥ 60 years [B2], n = 27). The median age was 52 years (range: 26-59 years) in group A1, 64 years (range: 60-71 years) in group A2, 48.5 years (range: 32-59 years) in group B1 and 64 years (range: 60-72 years) in group B2. All seven cycles were administered in 95% (A1), 100% (A2), 99% (B1), and 89% (B2) of patients. A dose reduction was made only in 1% (A1), 2% (A2), 1% (B1), and 1% (B2) of cycles. In comparing these four groups, delays in administering cycles...
were more frequent in the dose-intensified group of older patients (6% in A1 vs 17% in A2; 6% in B1 vs 11% in B2). The hematologic toxicity data are shown in Table 1. NCI-CTC grade 3/4 nonhematologic toxicities were rare and revealed no differences between the groups.

**CONCLUSION:**

The administration of a dosedense regimen with epirubicin and paclitaxel followed by CMF with G-CSF support is feasible in elderly patients with a tolerable safety profile. Referring to the analyzed data, a decreased hematopoietic potency must be considered in older patients.

**Commentary on Abstracts #A-36, #776, #677, #583, #552, and #589**

Jeffrey Crawford, MD

Lyman and colleagues (MASCC abstract #A-36, ASCO abstract #776) reported another very important outcome of neutropenia distinct from infection—the potential for reduced chemotherapy dose intensity in patients with early-stage breast cancer. Utilizing the prospective ANC registry that was described earlier, 600 patients were evaluated with early-stage breast cancer. In this cohort, 42% of patients developed ANC less than 500 or infection. Predictors for neutropenic complications included anthracycline-based regimens, and prior chemotherapy. In models for reduced relative dose intensity, both stage of disease and practice center were also significant independent predictors. By developing a tool to identify patients at risk for neutropenic complications, the investigators hope to develop a more rational use of growth factor support to improve chemotherapy dose delivery. Until better risk models are developed for primary prophylaxis, both colony-stimulating factors and secondary prophylaxis after a prior neutropenic event will remain a commonly used strategy to maintain dose intensity in early-stage breast cancer. Vogel and colleagues (ASCO abstract #677) identified 250 patients who received G-CSF in support of TAC chemotherapy. Eightyseven percent of those patients received G-CSF as a secondary prophylaxis. The rate of febrile neutropenia per cycle was 3.1% for patients receiving G-CSF with TAC compared to 6% of patients receiving TAC without the G-CSF. The authors concluded that for patients experiencing neutropenic events with TAC, secondary prophylaxis with G-CSF is appropriate. (As noted in the earlier section redefining the risk threshold of febrile neutropenia, TAC chemotherapy would be in the range of 20% and would qualify for primary prophylaxis.) In another report from six European audits of adjuvant breast cancer chemotherapy, Leonard and colleagues (ASCO abstract #619) found that neutropenic events were clearly associated with a likelihood of low relative chemotherapy dose intensity. In this review of 2,633 patients, an average relative dose intensity of less than 85% was observed in 14% of the population. Six percent of patients without neutropenic events experienced a low relative dose intensity vs 17% of patients who did experience a neutropenic event (P < .005). And what is the evidence that reducing dose intensity in adjuvant chemotherapy is detrimental to outcome in early-stage breast cancer? To address this, Delozier and colleagues (ASCO abstract #583) identified three groups of patients undergoing adjuvant FEC chemotherapy. According to protocol, chemotherapy was postponed for 1 week in patients who presented with leukopenia on day 1. In their study of 872 patients, 181 patients underwent all six cycles of therapy without delay (group 1). A total of 343 patients in group 2 experienced up to three treatment delays. Group 3 experienced more than three treatment delays and this accounted for 350 patients. The 4-year disease-free survival rate was 79.4%, 76%, and 66.1%, respectively, for the three groups. While the differences did not reach statistical significance (P = .09), the trend suggests that delivery of chemotherapy on time is an important variable. Furthermore, patients whose total treatment time exceeded 130 days did have a higher risk of relapse (P = .03). This provocative data,
along with previous studies by Bonadonna and the Cancer and Leukemia Group B, continues to emphasize the importance of chemotherapy dose delivery as an important predictor of outcome. Prospective trials with CSF support to maintain full-dose chemotherapy on time would provide definitive support of this principle. The importance of such a prospective trial is evidenced by other data from Tinker and colleagues (ASCO abstract #552). This group was unable to demonstrate that reductions in the dose of adjuvant AC chemotherapy in early breast cancer were associated with an impact on clinical outcomes. This retrospective analysis involved 484 patients receiving AC chemotherapy regimen. Whether or not the differences between this Canadian trial and the French study are due to differences in population, sample size, or the chemotherapy regimen can only be further defined by prospective studies. Lastly a phase III randomized trial was performed to compare the tolerability of dose-dense chemotherapy in older compared to younger breast cancer patients (ASCO abstract #589). Kuemmel and colleagues from Germany were able to demonstrate that four cycles of epirubicin and paclitaxel could be administered every 2 weeks along with three cycles of CMF chemotherapy with G-CSF support. Across a variety of subgroups of patients, only 1% to 2% of patients require dose reduction. In the older population, dose delays occurred more commonly during dose-dense therapy: 17% vs 6%. There were also more frequent dose delays in the older patients receiving every-3-week chemotherapy: 11% vs 6%. However, overall the authors concluded that a dose-dense chemotherapy regimen with G-CSF support is feasible in the elderly with a tolerable safety profile. Thus, in settings where dose-dense studies have been shown to be more efficacious, older women with breast cancer can be considered for such a strategy when appropriate.

Neutropenia and Lymphoma Abstract #8068
A Model to Predict Chemotherapy-Related Severe or Febrile Neutropenia in Cycle 1 Among Breast Cancer and Lymphoma Patients V. A. Morrison, V. Caggiano, M. Fridman, D. J. Delgado VA Medical Center, Minneapolis, Minnesota; Sutter Cancer Center, Sacramento, California; AMF Consulting, Los Angeles, California; Amgen Inc, Thousand Oaks, California Chemotherapy used to treat cancer may produce severe (absolute neutrophil count ≤ 250/mm$^3$) or febrile neutropenia, which often results in fever, infection, and hospitalization. This can lead to dose delays or reductions in subsequent chemotherapy cycles and/or early termination of therapy. Recent studies suggest most patients who experience severe febrile neutropenia do so early in the course of chemotherapy, in particular during the first cycle. Several recent risk models for neutropenia have identified baseline patient characteristics that predict the occurrence of neutropenia. The ability to identify patients at risk for developing neutropenia early in their therapy might help guide appropriate hematopoietic growth factor use. We evaluated possible risk factors associated with cycle 1 severe febrile neutropenia among a sample of patients with non-Hodgkin's lymphoma (NHL) or breast cancer. A historical case series of 1,617 patients (704 NHL and 913 early-stage breast cancer) who received initial chemotherapy at 16 community and academic oncology practices between 1991 and 1999 were selected for study. Severe febrile neutropenia was defined as an absolute neutrophil count ≤ 250/mm$^3$ or febrile neutropenia. A total of 461 patients (29%) experienced at least one episode of severe febrile neutropenia; 268 (58%) of these patients (167 [59%] with NHL and 101 [56%] with breast cancer) had severe febrile neutropenia in cycle 1. Risk factors associated with cycle 1 severe febrile neutropenia included age ≥ 65 years (odds ratio [OR] 2.08; 95% CI = 1.48-2.92); baseline hemoglobin < 12.0 g/dl (OR 1.90; 95% CI = 1.41-2.58); presence of heart, renal, or liver disease (OR 2.12; 95% CI = 1.03-4.36); NHL (OR 1.64; 95% CI = 1.16-2.32); planned full chemotherapy dose intensity (OR 2.74; 95% CI = 1.55-4.84); and no growth factor in the first 5 days of cycle 1 (OR 1.82; 95% CI = 1.07-3.08). CONCLUSION: Data routinely available to the clinician can help identify patients at risk for severe febrile neutropenia in cycle 1. In our model assessing chemotherapy-related severe febrile neutropenia in breast cancer and lymphoma, patients ≥ 65 were twice as likely to have severe febrile neutropenia in cycle 1. Abstract #A-60

Prevalence and Predictors of Febrile Neutropenia in Patients With Aggressive Non-Hodgkin's Lymphoma D. C. Dale, G. H. Lyman, J. Crawford, for the ANC Study Group University of Washington, Seattle, Washington; University of Rochester, Rochester, New York; Duke University, Durham, North Carolina Febrile neutropenia (FN) is a serious complication of chemotherapy that frequently requires hospitalization, dose reductions, and dose delays. As a consequence, FN may potentially compromise overall dose intensity and thus negatively impact long-term survival and the potential for cure. To evaluate the delivery of chemotherapy dose intensity, the incidence of FN, and the impact of demographic and clinical characteristics, we conducted a nationwide survey of 567 community oncology practices and analyzed the records of 4,522 patients with aggressive non-Hodgkin's lymphoma (NHL) receiving standard regimens of CHOP, CHOPrituximab (Rituxan), or CNOP. The average age of the study population was 61 years,
Febrile Neutropenia and Reduced Dose Intensity in Patients With Aggressive Non-Hodgkin’s Lymphoma Treated With CHOP and CNOP
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Myelosuppression remains the major doselimiting toxicity of systemic chemotherapy in patients with intermediate-grade non-Hodgkin’s lymphoma (NHL). Recent studies support the importance of sustaining dose intensity in this setting. A survey of 1,243 community oncology practices, including nearly 5,500 patients receiving chemotherapy for NHL, was undertaken to evaluate the impact of demographic, clinical-, and treatment-related factors on delivered dose intensity. Relative dose intensity (RDI) was estimated for each drug as the ratio of dose intensity to reference standard was 84%, with averaged planned and unplanned reductions in RDI of 4.5% and 11.5%, respectively. Forty-five percent of patients received average RDI < 85%. Risk factors for average RDI ≤ 85% included age ≥ 65 (53%), stage 4 (53%), ECOG performance status ≥ 2 (57%), female gender (48%), body mass index (BMI) ≥ 30 (50%), and hospitalization for febrile neutropenia (54%). Colony-stimulating factors were used in 41% of patients primarily in response to a previous episode of febrile neutropenia. In multivariate analysis, significant independent risk factors for average RDI < 85% included age > 65 (OR = 1.8), female gender (OR = 1.2), stage 4 (OR = 1.6), CHOP (OR = 1.3), BMI ≥ 30 (1.4) and previous febrile neutropenia hospitalization (1.4). CONCLUSION: Nearly half of patients with aggressive NHL histology treated with CHOP-like regimens experienced substantial dose reductions related to age, stage, gender, obesity, regimen, and previous febrile neutropenia hospitalization.}

Commentary on Abstracts #8068, #A-60, and #6599

Jeffrey Crawford, MD
In a study that overlaps both breast cancer and lymphoma, Morrison and colleagues (ASCO abstract #8068) developed a model to predict chemotherapy related severe or febrile neutropenia in cycle 1 among both breast cancer and lymphoma patients. Among 461 patients, 29% experienced at least one severe or febrile neutropenic episode. Of these episodes, 58% occurred in the first cycle of treatment. The risk factors identified for cycle 1 neutropenic complications included age greater than 65, baseline hemoglobin less than 12 g/dL, the presence of comorbidities related to heart, renal or liver disease, planned fulldose chemotherapy dose intensity, and no growth factor support in the first 5 days of cycle 1. These data come from a historical case series from 16 community and academic oncology practices and can be validated in other ongoing databases. In the abstracts by Dale and colleagues (MASCC abstract #A-60, ASCO abstract #6599), the prevalence and predictors of febrile neutropenia in patients with aggressive non-Hodgkin’s lymphoma were evaluated from a nationwide survey of 567 community oncology practices that identified 4,522 patients with aggressive non-Hodgkin’s lymphoma receiving CHOP or a CHOP-like regimen. The prevalence of febrile neutropenia in this overall population was approximately 20%, which would place CHOP as a regimen to be considered for a primary prophylaxis based on redefined risk threshold previously discussed. Furthermore, an even higher risk of febrile neutropenia occurred in patients over 60, those of female gender, those patients with stage III or IV disease, and those patients with an Eastern Cooperative Oncology Group performance status of 2 or greater, as well as
patients with a pretreatment absolute neutrophil count of less than $1 * 10^9/L$. Patients with a body surface area greater than $2 \text{m}^2$ and patients who started prophylactic CSF in the first cycle were at a reduced risk of febrile neutropenia. Thus, it appears that these two different studies in lymphoma have resulted in several similar characteristics that increased the patient's risk for febrile neutropenia. If a risk threshold of $20\%$ is used, most patients with aggressive lymphoma receiving a CHOP-like regimen will qualify for first-cycle prophylaxis. It is clear that these risks are even further elevated in the patient populations previously described. Other Uses of Colony-Stimulating Factors

**Abstract #6639**

**Pegylated Filgrastim After High-Dose Chemotherapy and Autologous Stem Cell Transplant**

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Pegylated filgrastim (PF) ($6 \text{mg}$ fixed dose) is equivalent to daily filgrastim ($5 \text{µg/kg/d}$ for 14 days) after chemotherapy in decreasing the duration of neutropenia. Daily filgrastim ($5 \text{µg/kg}$) started after high-dose chemotherapy (HDC) and autologous stem cell transplant (ASCT) leads to significant decrease in time to neutrophil engraftment. The role of PF after HDC and ASCT is not known. We propose to study the role of PF given as a single fixed dose ($6 \text{mg}$) subcutaneously (SC) on day +1 after stem-cell infusion. A total of 15 patients undergoing HDC and ASCT using peripheral blood stem cells for multiple myeloma or lymphoma have been enrolled in an ongoing study. Stem cells were collected with peripheral blood pheresis after cyclophosphamide ($3 \text{g/m}^2$) and daily filgrastim ($10 \text{µg/kg}$). All patients were eligible for HDC and ASCT as per institutional criteria, and consented. The conditioning regimens were highdose melphalan ($200 \text{mg/m}^2$) for myeloma, and cyclophosphamide ($7,200 \text{mg/m}^2$), BCNU ($400 \text{mg/g/m}^2$), and infusional etoposide ($2,400 \text{mg/m}^2$) for lymphoma. Patients received anti-infective prophylaxis with acyclovir, levofloxacin, and fluconazole starting day -1. Packed red blood cells (PRBC) and platelets were administered for a hematocrit and platelet count of less than $25\%$ and $20,000/\mu\text{L}$, respectively. There were no adverse events attributable to PF. All patients engrafted neutrophils and platelets. The median time to NE was 10 days (range: 8-11 days). Incidence of febrile neutropenia was $67\%$, with a median duration of 2 days (range: 1-4 days). Twentythree bacterial blood cultures were obtained in 10 patients for febrile episodes or a suspected line infection, with only 5 (in 5 patients) being positive, all for coagulase-negative staphylococcus. Antibacterials other than for prophylaxis was required in $60\%$ (9/15) of patients. Antifungals other than for prophylaxis were not required. The median time to platelet engraftment was 17 days (range: 14-19 days). The median number of transfusions was 3 units of PRBC and 12 units of platelets. The median days with mucositis and total parenteral nutrition were 3 (range: 0-9 days) and 3 (range: 0-12 days), respectively. CONCLUSION: Pegylated filgrastim at a fixed dose of $6 \text{mg}$ SC administered on day +1 after HDC and ASCT appears to be equivalent to daily filgrastim. Abstract #6634

**GM-CSF + Interferon-Alfa Induce a Graft-vs-Leukemia Effect in Bone Marrow Transplant Patients With Relapsed AML and ALL**

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Relapse of acute leukemia following allogeneic hematopoietic progenitor cell transplantation (HPCT) has a poor prognosis. Second HPCT and donor leukocyte infusions have significant toxicity with limited effectiveness. GM-CSF and interferon-alfa (IFN) activate dendritic cells and induce leukemia cells to express costimulatory molecules and enhance alloantigen presentation, potentially inducing graft-vs-leukemia effects. We hypothesized GM-CSF and IFN induce antileukemic effects in patients with relapsed acute leukemia. We performed a single-institution retrospective study of 97 patients with AML or ALL relapsed after allogeneic HPCT. The dose and duration of cytokines, toxicities, response, and postrelapse survival were analyzed. Overall survival rates of cytokinetreated patients were compared with relapsed leukemia patients who did not receive cytokine immunotherapy. Six patients received GM-CSF and IFN injections following the diagnosis of ALL or AML relapsed after allogeneic HPCT. The median dose of GM-CSF was $500 \text{µg}$ administered 3 times per week (median of six doses). The median dose of IFN was $3 \text{million units}$ administered 1 to 3 times per week (median of six doses). Four of the six patients (67%) exhibited a pathologic or hematologic remission with an average response of 3.3 months (range: 6 weeks to 12 months) Toxicities included malaise, myalgias, and fever. Graft-vs-host disease was documented in four of the six patients, and occurred at a median of 6 weeks after beginning cytokine immunotherapy. The median survival of cytokine-treated patients was 130 days, with three of six patients remaining alive at a median follow-up of 373 days. Two of three surviving patients remain without evidence of disease on no immunosuppressive drugs. Cytokinetreated patients had better survival compared to 91 noncytokine-treated patients with relapsed ALL or AML (median survival of 52 days, 1-year survival of $8\%$, $P = .02$). CONCLUSION: The administration of GM-CSF and IFN may induce remissions in
patients with acute leukemia who have relapsed after allogeneic HPCT. Further studies to evaluate the optimal dosing schedule and duration of therapy should be pursued. Abstract #6612

Priming GM-CSF and Low-Dose Cytarabine in the Treatment of High-Risk and Elderly Acute Myelogenous Leukemia and Myelodysplastic Syndrome Patients E. S. Winer, K. B. Miller, G. W. Chan Tufts-New England Medical Center, Boston, Massachusetts; Beth Israel Deaconess Medical Center, Boston, Massachusetts Priming of leukemic cells with cytokines may enhance the efficacy of cell cycle chemotherapy. We attempted to use GM-CSF to enhance the effects of low-dose cytarabine to increase cell recruitment, and optimize cell cycle chemotherapy in patients unable to tolerate conventional induction chemotherapy. We evaluated the efficacy of GM-CSF priming with low-dose cytarabine and concomitant hydroxyurea in high-risk, elderly AML and advanced MDS patients. Patients received induction chemotherapy with GM-CSF 250 μg/m²/d by continuous infusion days 1-7, hydroxyurea 500 mg po qid day 1 and 500 mg po tid days 2-15, and cytarabine 20 mg/m²/d by continuous infusion days 2-15. Forty-nine patients (26 female, 23 male) were treated, median age 68.5 years (range 48-85); 78% had no previous treatment, and 22% of patients had a median of two prior treatments (range: 1-7). All patients were not eligible for standard induction chemotherapy. Following treatment, 44% of the assessable patients had documented aplastic bone marrows. The overall response rate was 49%; 33% with CR and 16% with PR. Median duration of CR was 251 days (range: 36-842 days). The CR for secondary AML was 18%, for de novo AML 38%, and for MDS 67%. None of the patients developed mucositis or alopecia, and no patient had greater than grade I nausea and vomiting. The most common adverse effects were neutropenic fever (68%), atrial fibrillation (7%), and congestive heart failure (5%). Five patients died of treatment-related toxicity (sepsis). The median survival for all patients was 150 days, for patients achieving CR was 290 days, and the 1-year survival rate was 24%. CONCLUSION: GM-CSF priming can enhance the cytoadjuvant effects of low doses of cytarabine. This combination therapy is well tolerated, and should be explored as an alternative regimen for high-risk and elderly AML and advanced MDS patients. Commentary on Abstracts #6639, #6634, and #6612

Jeffrey Crawford, MD This commentary has focused on our understanding of the role of colony-stimulating factors, particularly G-CSF and pegfilgrastim, in the management of chemotherapy-induced neutropenia- both to reduce the risk of neutropenic complications and to improve chemotherapy dose delivery in appropriate settings. For the readership, however, it should be noted that the impact of colony-stimulating factors and potential applications extend to many other therapeutic settings. In ASCO abstract #6639, Jagasia and colleagues describe the use of pegfilgrastim after high-dose chemotherapy in autologous stem cell transplant. In this setting, a single fixed dose of 6 mg SC administered on day +1 after high-dose chemotherapy and autologous stem-cell transplant appeared to be equivalent to prolonged daily filgrastim. Thus, even in a setting of prolonged neutropenia, the steady-state concentrations of pegfilgrastim during neutropenia result in this very favorable pharmacodynamic effect. In addition, GM-CSF was evaluated as part of a therapeutic approach, along with interferon alfa, to induce a graft-vs-leukemia effect in bone marrow transplant with relapsed AML and ALL. In this study by Arellano (ASCO abstract #6634), this therapeutic combination induced remissions in patients with acute leukemia after relapse from allogeneic transplant, and provides an encouraging strategy. Another abstract looked at priming with GMCSF and low-dose cytarabine in the treatment of elderly AML and myelodysplastic syndrome patients. This study by Weiner and colleagues (ASCO abstract #6612) demonstrated that GM-CSF priming could enhance cytoadjuvant effects of low doses of cytarabine. These two small trials suggest some interesting and novel directions for the use of GM-CSF. As further studies evolve, these applications of GM-CSF may provide an important niche for this multipotent cytokine.

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4. Holmes FA, O'Shaughnessy JA, Vukelja et al: Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as the adjunct to

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