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INSIDE

Inadequate Lymph Node Resections in Colorectal Cancer Surgery

ABSTRACT & COMMENTARY

Synopsis: *Most authorities agree that the minimal number of lymph nodes resected in primary colorectal cancer surgery is 12. This allows adequate evaluation and more accurate staging. In an examination of SEER data for colorectal cancer patients without known distant metastases during the years 1988 through 2001, the median number of nodes resected was 9, and in only 37% was the standard of 12 nodes achieved. Age, tumor site, and geographic location were statistically important factors accounting for some of the variability. The implications of inadequate lymph node resection are considerable with regard to clinical trial validity and overall clinical outcome.*

Source: Baxter NN, et al. *J Natl Cancer Inst*. 2005;97:219-225.

LYMPH NODE STATUS IS THE STRONGEST PREDICTOR OF LONG-TERM outcome in patients with colorectal cancer who are without demonstrable distant metastatic disease. It would stand to reason that the number of lymph nodes resected would correlate with the accuracy of surgical staging. Accordingly, both the International Union Against Cancer and the American Joint Committee on Cancer have recommended the evaluation of at least 12 lymph nodes for adequate staging, and this has become a standard.[1,2]

Baxter and colleagues from the universities of Minnesota and Michigan used data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program to determine the proportion of colorectal cancer patients in the United States for whom surgical resection met this standard of 12 resected lymph nodes. Within the SEER registry between the period of 1988 to 2001, 116,995 colorectal cancer patients underwent radical surgery without prior neoadjuvant radiation. For the entire population, the median number of lymph nodes removed was 9 and in only 37% of patients was the standard of 12 met. The proportion of patients receiving adequate lymph node evaluation increased from 32% in 1988 to 44% in 2001, a significant trend ($P \leq 0.001$). Older patients

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(> 70 years) were less likely to receive adequate lymph node evaluation than younger patients and similarly, those with left sided or rectal cancers were less likely than those with right sided lesions to have adequate node sampling. Geographic location within the United States was also a source of significant variability. For the 11 SEER reporting centers, the range in success at resecting 12 lymph nodes varied from 33% to 53%. Thus, as recent as 2001, the majority of patients with colorectal cancer received inadequate lymph node evaluation. The association of demographic factors such as patient age and geographic location was interpreted by the investigators to suggest that local surgical and pathology practice patterns may affect the adequacy of lymph node evaluation for colorectal cancer patients.

COMMENT BY WILLIAM B. ERSHLER, MD

This report highlights the importance of adequate lymph node evaluation for optimal management of colorectal cancer patients. In a multivariate analysis, after adjusting for confounders, younger patients, patients with right-sided colon cancer, patients with Stage II or III disease, and patients with poorly differentiated tumors were statistically more likely to receive adequate lymph node evaluation than older patients, those with left sided lesions, those with Stage I disease, or those with well, or moderately well, differentiated tumors ($P < 0.01$ for all variables). Nonetheless, even under the most optimal of these conditions, a large share of the patients receive inadequate lymph node assessment.

Before commenting on the reasons for this, it is important to examine the rationale for setting the standard at 12 nodes. An inadequate lymph node evaluation is associated with worse outcome in terms of tumor recurrence and patient survival.[3-6] This may be because patients who are inaccurately identified with Stage II disease may not receive adjuvant therapy. In fact, some have suggested that patients deemed lymph node negative (Stage II) on the basis of a low number of retrieved negative nodes should be considered at high risk for tumor recurrence and considered candidates for adjuvant therapy.[5] Furthermore, it is possible that the retrieval of a small number of nodes is an indication of suboptimal surgical technique and that in itself may place the patient at higher risk for recurrence.

An additional concern relates to clinical trials. As a result of a developing consensus regarding the adequacy of surgical staging and the ultimate influence of accurate staging on outcome, some authors have recommended that node-negative patients with fewer than 12 lymph nodes examined be routinely excluded from surgical or adjuvant therapy trials.[4]

An explanation for why there is such a high rate of inadequate lymph node sampling is complex. Variability in the actual number of nodes available and other patient factors such as obesity (which hinders node identification) no doubt explains some of the finding. Yet, the geographic variability, the effect of patient age and the site of tumor (left vs right) are harder to explain but suggest that modifiable procedural factors may be involved. Indeed, within single institutions, educational programs targeted at both surgeons and pathologists have been successful. For example, Smith and colleagues reported[7] such an effort that resulted in a greater than doubling of the number of resected nodes (from 8 to 18) for Stage II colorectal cancer patients and the increased rate was sustained even 30 months after the program.

Thus, the majority of colorectal cancer patients in the United States receive inadequate surgical/pathological staging on the basis of too few evaluable lymph nodes. In order to improve treatment outcomes and the validity of clinical trial findings, this inadequacy needs to be corrected. ■

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Weekly Paclitaxel as First-Line Chemotherapy in Elderly Advanced Breast Cancer Patients

ABSTRACT & COMMENTARY

Synopsis: *Weekly paclitaxel is highly active in elderly advanced breast cancer patients. Data on cardiovascular complications, however, indicate the need for a careful monitoring of cardiac function before and during chemotherapy.*

Source: Del Mastro L, et al. *Ann Oncol*. 2005;16(2):253-258

There is a need to find effective and tolerable regimens for elderly patients with advanced breast cancer. Breast cancer is the most common cancer in women and its incidence increases with age. Despite the fact that it is a very common disease amongst women older than 65 years of age, their enrollment in clinical trials, particularly involving chemotherapy, has been negligible.[1] Reports indicate that elderly women receive less optimal surgery and less dose intensity chemotherapy although the data suggest that there is a benefit from chemotherapy though smaller compared with patients younger than 50.[2,3] The taxanes have been established as vital components of breast cancer treatment both in the adjuvant and metastatic meeting. Weekly paclitaxel has been developed as an alternative to the standard every-3-week dosing schedule and has been shown to have a favorable toxicity profile as well as increased efficacy.[4-6] This current trial evaluates weekly paclitaxel in women with metastatic breast cancer 70 years of age and older.

COMMENT BY STUART M. LICHTMAN, MD

The eligibility of the trial was women with histologically or cytologically confirmed metastatic (stage IV) or locally advanced (stage IIIA, IIIB) breast cancer who were age 70 years and older. Prior chemotherapy for their metastatic or locally advanced disease was not allowed. Previous adjuvant chemotherapy not containing taxanes (paclitaxel or docetaxel), and prior endocrine therapy were allowed. The other eligibility criteria were an adequate performance status (Eastern Cooperative Oncology Group 0-2), the absence of brain metastases and adequate bone marrow, renal, and liver function. At baseline a multidimensional geriatric assessment was performed.[7,8] Comorbidities were scored as absent/present using a predefined list of 33 possible diseases. Geriatric scales, namely those exploring activities of daily living (ADL) and instrumental ADL (IADL) were also used. Response codes range from 0 (full ability) to 8 (full disability) for the IADL scale and from 0 to 6 for the ADL scale. The study was designed as a multicenter, 2-stage, phase II study with activity and toxicity as primary end points. The primary objective was to evaluate the activity (response rate) and toxicity (within the first 4 cycles) of weekly paclitaxel. Paclitaxel 80 mg/m^2 was administered intravenously over 1 h weekly for 3 weeks every 28 days.

Forty-eight eligible patients had been enrolled by 7 participating centers. The median age was 74 years. Presence of comorbidities at baseline was assessed in 41 patients, and hypertension, arthrosis-arthritis, osteoporosis, arrhythmias and peripheral vascular disease were the most common comorbidities. Based on comorbidity data, 26 patients (63.4%) had none of the diseases used for the calculation of the Charlson scale (Charlson index 0). Baseline ADL and IADL data were available for 38 and 36 patients, respectively; at least one ADL dependency was reported in 10 (26.3%) patients and IADL dependency in at least one item was reported in 25 (73.2%) patients.

All 46 patients who received at least one administration of chemotherapy were evaluated for toxicity. Unacceptable toxicity within the 4 four cycles occurred in 7 patients (15.2%) and was represented by one case of febrile neutropenia associated with lung infiltrates, one case of severe allergic reaction and 5 cases of cardiac toxicity, including 2 patients who died, one with pulmonary embolism 2 days after chemotherapy (third cycle) and one with congestive heart failure 26 days after administration of the second cycle. Two additional cases of severe cardiotoxicity (one case of grade 2 and one of grade

3) occurred after the fifth cycle. Clinically relevant hematological toxicity was uncommon, with 2 cases of febrile neutropenia (including the one considered as unacceptable according to study design), one of grade 4 neutropenia, one of grade 3 thrombocytopenia, and one of grade 3 anemia. This grade 3 anemia was present at baseline and was not considered as unacceptable toxicity. Grade 2 sensorial neuropathy occurred in 33% of patients. One patient, with concomitant cholelithiasis, had an increase in gamma-glutamyl transpeptidase value that was classified as grade 3 liver toxicity.

A complete response occurred in 2 (4.9%) patients and a partial response in 20 (48.8%), with an overall response rate of 53.7% and 11 patients (26.8%) had disease stabilization. Among the 9 patients with locally advanced breast cancer there were 8 partial responses (response rate, 88.9%) and 1 stable disease. Among 32 patients with stage IV disease, there were 2 complete and 12 partial responses, for a response rate of 43.8%. Median progression-free survival was 9.7 months and median survival was 35.8 months. Unplanned subgroup analyses were performed to generate hypotheses regarding the possibility that geriatric assessment can help to predict toxicity and activity of treatment. The Charlson and the IADL scales were not predictive of either toxicity or activity. However, the presence of at least one inability among those items in the ADL scale was significantly associated with both a lower probability of response (P = 0.009, Fisher's exact test) and a shorter progression-free survival (P = 0.04, log-rank test), but not with unacceptable toxicity rates.

This phase II trial focused exclusively on elderly patients, and its design took into account both toxicity and activity as criteria for recommendation about the treatment with weekly paclitaxel. There was cardiovascular toxicity observed in 5 patients ranging in grade from grade 2 to 5. Two patients had a decrease in resting ejection fraction, 1 patient had acute myocardial infarction and 2 patients had fatal cardiovascular toxicity consisting of congestive heart failure (1 patient) and pulmonary embolism (1 patient). Two additional patients developed severe cardiotoxicity (one grade 2 and one grade 3) after the fifth cycle. In addition, grade 1 cardiotoxicity (ie, asymptomatic decline of resting ejection fraction ≥10% but ≤ 20% of baseline value) was observed in 5 patients (11%). Overall, cardiotoxicity of any grade developed in 12 patients (26%). Specifically, grade 5, 4, 3, 2 and 1 cardiotoxicity occurred in 2 (4%), 1 (2%), 1 (2%), 3 (7%) and 5 (11%) patients, respectively. No cases of cardiotoxicity were observed in previous studies with weekly paclitaxel administered in metastatic breast cancer patients.[6,10] However the majority of the events (8 out of 12; 67%) were grade 1 (5 cases) and grade 2 (3 cases) cardiotoxicity, ie, laboratory decline of resting ejection fraction without clinical symptoms.

These events were recorded because a routine MUGA or echocardiographic evaluation was performed in this study every 2 cycles. In the previous studies and in routine clinical practice this is not carried out. A major risk of developing cardiotoxicity is older age. The median age of patients in this trial was 74 years (range, 70-87) compared with a mean age of 60 years (range, 31-88) reported in the study by Perez et al and a median age of 57 years (range, 35-74) in the study by Seidman et al.[6,9] Other cardiotoxicity risk factors, such as hypertension, were present in up to 63% of patients. These differences in patients' characteristics may explain this observation. This points out the importance of doing trials specifically in this older population.

The observed response rate of 54% is similar to that recently reported with weekly paclitaxel in a phase III study not focused on elderly patients, ie, 40%.[4] These data indicate that weekly paclitaxel is a highly active treatment in elderly patients with advanced breast cancer. The data on cardiovascular complications are interesting and important and deserve further study. However they do not detract from the potential benefit of this therapy for older patients. ■

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Rethinking Bone Marrows: Are They Necessary in Early Stage Diffuse B-Cell Lymphomas?

ABSTRACT & COMMENTARY

Synopsis: *In a retrospective analysis of approximately 200 patients with early stage B-cell diffuse lymphoma, bone marrow aspirate and biopsy revealed involvement in only 3.6%. A review of a number of risk factors indicated 3 (low hemoglobin, low white blood count, and bulky disease) as predictors of marrow involvement. In fact, the absence of these 3 factors gave a negative predictive value of 99.2% for marrow involvement. The study concludes that bone marrow sampling may be safely omitted in early stage diffuse B-cell lymphoma in selected patients (those without the 3 mentioned risk factors).*

Source: Lim ST, et al. *Ann Oncol*. 2005;16:215-218.

In the evaluation of newly diagnosed lymphoma, bone marrow aspirate and biopsy are typically performed in an effort to most accurately stage patients and, thereby, design therapy. Although this procedure is safe, it is frequently uncomfortable for the patient and a source of anxiety and expense.[1,2] Lim and colleagues report a retrospective analysis of 192 patients treated at the National Cancer Centre of Singapore. These patients were found to have stage I or II disease after clinical and CT scanning before bone marrow analysis. Clinical data were catalogued, including age, sex, presence of B symptoms, white blood count (WBC), platelet count, hemoglobin, serum lactate dehydrogenase (LDH), serum 2-microglobulin (B2M) , presence of extranodal disease, presence of bulky disease (defined as tumor diameter of > 7 cm) and radiological stage. A low hemoglobin was defined as < 10 g/dL; a low WBC as $<4 \times 10^9$/L, and a low platelet count as $< 100 \times 10^9$/L. Bone marrow was considered involved if either the aspirate or trephine biopsy showed the presence of lymphomatous infiltrate by standard morphological assessment.

Overall, bone marrow involvement was found in 7 patients (3.6%). Comparing the clinical measures between patients with and without marrow involvement, a low hemoglobin ($P = 0.02$), low WBC ($P = 0.007$) and bulky disease ($P = 0.006$) were associated with bone marrow involvement. Among the 120 patients without bulky disease, a hemoglobin level of more than 10 g/dL and a WBC of $> 4 \times 10^9$/L, only one patient had bone marrow involvement (0.83%; 95% CI, 0.02%-4.6%). The presence of any of the 3 risk factors (low hemoglobin, low WBC, or bulky disease) gave a positive predictive value of 8.3% for bone marrow involvement whereas the absence of all 3 factors gave a negative predictive value of 99.2% for bone marrow involvement.

COMMENT BY WILLIAM B. ERSHLER, MD

This was a careful retrospective analysis with some practical findings for the clinician. However, currently patients undergoing staging for lymphoma will have marrow aspirate sent for flow cytometry or even for PCR analysis looking for rearrangement of the immunoglobulin gene. These measures are likely to be more sensitive than routine histological examination alone, and thus might have yielded a higher than 3.5% marrow involvement in this same series.

That stated, outside of a research setting the need to be absolutely certain whether bone marrow is involved is germane only if treatment hinged on the results. In this regard the recent follow-up from the Southwest Oncology Group (SWOG) trial in which 401 patients with limited stage aggressive lymphoma were randomized to either 8 cycles of CHOP chemotherapy or 3 cycles followed by involved field radiation is of importance. Although the early analysis[3] showed an advantage for those randomized to the combined modality treatment, the long-term follow up demonstrated an increase in late relapses and lymphoma-related deaths in patients receiving short-course chemotherapy and involved field radiation.[4] One might conclude from this study that even patients with early stage diffuse B-cell lymphoma should be treated with chemotherapy alone, and thus bone marrow aspirate would be a non-essential component of the pretreatment evaluation. Clinicians are keen on having as much information as possible before starting treatment. However, in balance, the avoidance of the significant anxiety and pain associated with the marrow procedure may over shadow the importance of the findings (positive or negative) in patients for whom the treatment will likely be the same under either circumstance. The study from the Singapore Cancer Centre is reassuring that for selected early stage patients (those with normal blood counts and non-bulky disease), less than 1% would have been positive if the procedure were performed. ■

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Docetaxel and Continuous-Infusion Fluorouracil vs Epirubicin, Cisplatin, and Fluorouracil for Advanced Gastric Adenocarcinoma

ABSTRACT & COMMENTARY

Synopsis: *The combination of docetaxel and fluorouracil (DF) was compared with epirubicin, cisplatin and fluorouracil in a randomized Phase II trial in the treatment of advanced gastric cancer. The combinations proved equally efficacious but the toxicity profiles favored DF, with less nausea and vomiting. DF appears to be a promising regimen for this disease.*

Source: Thuss-Patience PC, et al. *J Clin Oncol*. 2005;23:494-501.

There remains no standard chemotherapy regimen for advanced gastric adenocarcinoma. Thuss-Patience and colleagues from Germany conducted a multicenter, randomized, phase II study for patients with advanced disease comparing 2 regimens (docetaxel and fluorouracil [DF] vs epirubicin, cisplatin, and fluorouracil ECF]). For the DF arm, docetaxel was administered at 75 mg/m^2 on day 1 and fluorouracil was 200 mg/m^2 by continuous infusion for days 1-21 of a 21 day cycle. For ECF, epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 were given on day 1 and fluorouracil was given at 200 mg/m^2 on days 1-21 of a 21-day cycle.

Ninety patients were randomized and, in both arms, 43 of 45 patients were evaluable. In the DF arm, two patients (4.4%) experienced a confirmed complete tumor remission and 15 patients (33.3%) experienced a confirmed partial remission for an overall response rate (ORR) of 37.8%; 95% confidence interval (CI), 25.9%-51.9%. Two patients in the ECF arm (4.4%) showed confirmed complete remission and 14 (31.1%) showed confirmed partial remission (ORR, 35.6%; 95% CI, 24.8%-48.7%). Median survival was 9.5 and 9.7 months and the median time to tumor progression was 5.5 and 5.3 months for the DF and ECF arms respectively.

Although the toxicity was rarely severe, the profiles were different for the 2 treatment regimens. Major toxic effects included diarrhea, stomatitis, and leukopenia for the DF treated patients whereas it was nausea, vomiting and leukopenia for the ECF treated patients.

Thuss-Patience et al concluded that DF can be safely administered and that the regimen may prove to be less toxic by virtue of avoiding cisplatin.

COMMENT BY WILLIAM B. ERSHLER, MD

Although there is no standard treatment regimen for advanced gastric cancer, cisplatin-containing regimens are frequently employed in some combination with fluorouracil.[1,2] ECF has been demonstrated to be an active combination and was superior to fluorouracil, doxorubicin, methotrexate (FAMTX)[3] and this regimen has gained widespread use in this setting. However, toxicity has been problematic and alternative regimens are continuously sought for either improved efficacy or diminished toxicity.

In this light, the current phase II trial offers promise. The DF regimen has theoretical appeal because the drugs have demonstrated synergism in tumor models and, for the most part, toxicity is not overlapping. This is particularly true if the 21-day infusion of fluorouracil is chosen, as this has been shown to be associated with less myelotoxicity, a potential problem when fluorouracil is used with docetaxel. Indeed, although leukopenia was observed, it was comparable with ECF and manageable.

Of note, with regard to toxicity, the findings indicate a different profile between the 2 groups, with significantly less nausea and vomiting in the DF arm. By excluding cisplatin, it is likely that administration is less complex and the debilitating gastrointestinal toxicities diminished. These features, in light of the comparable efficacy to ECF, both in this study and from that reported in the literature, would suggest that DF is an appealing alternative to the commonly used cisplatin regimens, particularly in the out patient setting. Yet, the continuous infusion of fluorouracil remains a cumbersome approach, and one can't help but wonder whether capecitabine might be equally efficacious in either of these regimens as a substitute. Hopefully, this notion will ultimately be tested in a well constructed clinical trial. ■

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Secondary Surgical Cytoreduction for Advanced Ovarian Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *For patients with advanced ovarian carcinoma in whom primary cytoreductive surgery was considered to be maximal, the addition of secondary cytoreductive surgery to postoperative chemotherapy with paclitaxel plus cisplatin does not improve progression-free survival or overall survival.*

Source: Rose PG, et al. *N Engl J Med*. 2004;351(24): 2489-2497.

Nearly 10 years ago, a randomized trial of interval cytoreduction for primary therapy of advanced ovarian cancer was published, suggesting the surgical intervention after 3 cycles of cisplatin and cyclophosphamide added significantly to progression-free (PFS) and overall survival (OS). Rose and colleagues, on behalf of the Gynecologic Oncology Group (GOG), reported final results on a similarly designed trial, which, unfortunately, leaves the question as to its benefit unresolved. In this trial, patients who were left with more than 1 cm of residual disease after an initial debulking effort were randomized to a second procedure if they were found not to progress during 3 cycles of paclitaxel and cisplatin adjuvant chemotherapy. Patients in both cohorts received a total of 6 cycles of chemotherapy. More than 400 patients were randomized. Relative to those patients receiving only one operation and adjuvant chemotherapy, those who had undergone the additional interval cytoreduction had similar PFS and OS. Hazard ratios for both events were statistically insignificant. Rose et al concluded that in the setting of a maximal initial attempt at cytoreduction plus paclitaxel and cisplatin chemotherapy no benefit was realized for an interval secondary procedure.

COMMENT BY ROBERT L. COLEMAN, MD

Most health care providers with even a peripheral understanding of ovarian cancer would most likely be able to articulate the importance surgery and chemotherapy play in the disease's management. These modalities represent the virtual *1-2 punch* of initial therapy for most cases of advanced disease. And, in general, the more *1* and possibly, the more *2*, that is realized, the better the outcome. However, as many as 20-50% of stage III and more stage IV patients are left with gross residual disease (> 1 cm) after primary exploration, usually the result of massive intraperitoneal carcinomatosis or intraparenchymal disease. Observational trials of chemotherapy before surgery for medically infirmed or other such non-surgical patients has demonstrated that a proportion achieve dramatic reduction in disease volume and in some cases, make those patients good candidates for debulking where favorable perioperative clinical courses are realized. Therefore, the question arose that if one could not achieve a complete resection initially, could this be achieved at a later point, particularly among those demonstrating a good response to chemotherapy, and thus improve their survival? Our initial insight into this question was "yes."[1] However, these data came as much of the treated population was receiving taxane-based chemotherapy regimens and the results from a confirmatory trial, while launched, was years away. The current study by Rose et al, employing a more contemporary treatment program, did not confirm the earlier encouraging data and left us sorting through the details of each study to determine why.

As pointed out by Rose et al, one key difference, besides the treatment regimen, lies in the intent of the initial surgery. In the initial trial, a cohort of patients could have entered the trial after disease documentation from only a biopsy. In this group of patients, the *interval surgery* more accurately represented the *initial* debulking attempt and the chemotherapy, a neoadjuvant infusion. In addition, more stage IV patients were included in the initial trial, which may have contributed to the almost twice as frequent progression before interval surgery (9% vs 5%). Since these patients did not undergo surgery, a case selection bias of sensitive, but incompletely resected patients populated the initial trial. This is most evident by observing the significantly longer progression-free survivals in the initial trial compared to the GOG trial (18 mos vs 10.5 mos, interval reduction arm) but likely no difference in overall survival (26 mos vs 32 mos, interval reduction arm). In addition, consolidation therapy was allowed in the initial trial, but not in the GOG trial. Whether consolidation therapy truly affects the survival end points is unconfirmed at this time. However, at least one trial has suggested a progression-free survival advantage with the addition of 12 cycles of paclitaxel.[2]

So how does one interpret this clinical conundrum? A reasonable conclusion is that one maximal attempt at cytoreduction is warranted in the initial setting. Those left suboptimal don't appear to gain measurably with a second attempt after induction chemotherapy. Unclear biological characteristics are more likely at work in this situation and are an active focus of research.[3] Whether delaying surgery until the documentation of chemosen-

sitivity (neoadjuvant chemotherapy) will ultimately help our patients both in morbidity and survival is the subject of an ongoing randomized European trial. ■

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CME Questions

6. **When comparing DF (docetaxel and fluorouracil) with ECF (epirubicin, cisplatin and fluorouracil) for advanced gastric cancer, which of the following statements is true?**
   a. DF produced a significantly greater overall response rate and survival and was associated with less toxicity.
   b. DF was comparable with regard to overall response and survival but had less toxicity.
   c. DF was less effective with regard to overall response rate and survival but had less toxicity.
   d. DF was comparable with regard to overall response and survival but had greater toxicity.

7. **For patients with early stage (I or II) diffuse B cell lymphoma on the basis of clinical examination and CT scans, the likelihood of bone marrow involvement, as detected by morphological examination is:**
   a. 45-50%.
   b. 25-30%.
   c. 3-5%.
   d. Less than 1%.

8. **Which of the following is *not* associated with lower numbers of lymph nodes evaluated after colorectal cancer surgery?**
   a. Age
   b. Race
   c. Geographic location
   d. Anatomic location

Answers: 6 (b); 7 (c); 8 (b)

In Future Issues:

Femara and Adjuvant Breast Cancer Treatment

PHARMACOLOGY WATCH

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The Risk of Aspirin Withdrawal in ACS Patients

Stopping aspirin may be hazardous to your health, according to recent research. Patients with heart disease who developed acute coronary syndrome (ACS) were questioned to determine whether their aspirin therapy had recently been interrupted. Thirteen percent of patients with recurrent ACS had stopped aspirin within the previous month. The incidence of ST-segment elevation ACS was higher in those who stopped aspirin, compared to those who did not stop aspirin (39% vs 18%; *P*=0.001). The risk of stopping aspirin was particularly high for patients who had uncoated stents. The mean delay between aspirin withdrawal and acute coronary event was 10 days. Patients withdrew from aspirin for a number of reasons including minor surgery, endoscopy, dental treatment, bleeding, and noncompliance. The authors conclude that aspirin withdrawal in patients with coronary disease represents a risk for the occurrence of a new coronary event (*J Am Coll Cardiol.* 2005;45:456-459). The risk of ischemic stroke may be as much as 3 times higher with interruption of aspirin therapy, according to presentation at the International Stroke Conference. Researchers from Switzerland noted that the odds ratio for stroke or TIAs associated with aspirin discontinuation was 3.25 (95% CI). Seventy-seven percent of ischemic strokes related to aspirin discontinuation occurred in the first 8 days after aspirin was stopped, with remaining strokes occurring from day 9 to day 30. The reasons cited for discontinuing aspirin were primarily minor bleeding and minor surgical procedures—many of which can safely be performed (many dental procedures, cataract surgery among others) while patients are taking aspirin (strokeconference.americanheart.org /portal /strokeconference/sc/02.02.05c).

Neuropsychiatric Symptoms of Dementia

Treatment of neuropsychiatric symptoms in patients with dementia represents one of the biggest challenges in primary care. Dementia is diagnosed by the loss of cognitive function, but other symptoms are often more prominent including agitation, aggression, delusions, hallucinations, repetitive vocalizations, and wandering, among others. Many classes of psychiatric medications are used to treat neuropsychiatric symptoms in dementia including antidepressants, anxiolytics, anticonvulsants, cholinesterase inhibitors, typical antipsychotics, and atypical antipsychotics. Often these drugs are used in combination, and the cocktail can get confusing and even dangerous for patients and caregivers alike. A new review of the topic in the "Clinician's Corner" section of the February 2nd *Journal of the American Medical Association* helps clarify treatment options. The authors reviewed 29 articles that met their inclusion criteria. Among typical antipsychotics, which

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include haloperidol, thiothixene, chlorpromazine, trifluoperazine, and acetophenazine, there was no difference in the efficacy among these drugs in treating neuropsychiatric symptoms. Haloperidol may be somewhat more effective for treating aggression but not agitation. Side effects including extrapyramidal symptoms and somnolence are common with these agents. Antidepressants, including the SSRIs, were also relatively ineffective, except for treatment of depression associated with dementia. The best evidence for efficacy was found in the atypical antipsychotic group, especially risperidone (Risperdal) and olanzapine (Zyprexa). These drugs were found to have a modest effect on agitation/aggression, hallucinations, and delusions. A higher risk of stroke was found in the most recent trial (prompting a "Dear Doctor" letter from Janssen in April 2003). The cholinesterase inhibitors group including galantamine (Reminyl), donepezil (Aricept), and rivastigmine (Exelon) were somewhat disappointing with regard to neuropsychiatric symptoms, with minimal improvement of questionable clinical benefit. Memantine, the relatively new N-methly-D-asparte antagonist was seen to improve cognitive and functional parameters, but also did not improve neuropsychiatric symptoms. The authors stress that the management of neuropsychiatric symptoms in dementia "should always begin with an assessment of the medical (eg, pain and delirium) and environmental causes of the behavior." They also recommend starting with a cholinesterase inhibitor if the patient is not already receiving one, because they are relatively well tolerated and may benefit cognition and function (*JAMA.* 2005;293:596-608).

FDA Actions

Pfizer has received FDA approval to market pregabalin (Lyrica) for the treatment of painful diabetic neuropathy and post-herpetic neuralgia, the 2 most common types of neuropathic pain. Pregabalin was shown to be effective in a company-sponsored study of 338 patients with a 1-5 year history of painful, diabetic, peripheral neuropathy who were randomized to receive the drug at 1 of 3 doses or placebo for 5 weeks. Patients in the 300 and 600 mg/day doses showed improvements in mean pain score vs placebo ($P = 0.0001$), but no improvement was seen at the 75 mg/day dose. The higher doses also resulted in improvements in weekly pain score, sleep interferes score, patient global impression of change, clinical global impression of change, and lifestyle surveys. The most common side effects were dizziness and somnolence (*Neurology.* 2004;63:2104-2110). Pregabalin is a 3-substituted analogue of gamma-amino butyric acid (GABA), and is closely related to Pfizer's gabapentin (Neurontin), which recently lost its patent and is now available as a generic. Pregabalin is currently under review by the FDA for the treatment of partial seizures.

The FDA has also approved palifermin (Kepivance-Amgen) to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies undergoing chemotherapy, with or without radiation, in preparation for bone marrow transplantation. The drug, which is the first agent to be approved for this indication, stimulates epithelial cell growth in mucous membranes. It is given prior to fractionated total body irradiation and high dose chemotherapy, and repeated after bone marrow transplantation. The drug's efficacy in non-hematologic malignancies has not been shown.

Citalopram (Celexa) is now available in generic tablets and liquid. The liquid formulation recently joined the tablet formulation for the popular SSRI antidepressant.

Extended release buproprion (Wellbutrin SR) is now available as a generic in the 200 mg strength.

Fosinopril/HCTZ (Monopril) has also joined the generic ranks in 10/12.5 mg and 20/12.5 mg strengths.

The FDA has also approved a generic fentanyl transdermal system (Duragesic) for the treatment of severe chronic pain. The new generic, which is produced by Mylan technologies, provides a constant dose of the drug for 72 hours.

Canada has suspended marketing of Adderall and Adderall XR because of reports of sudden unexplained death (SUD) in children taking the drugs. SUD has been associated with amphetamine abuse and has been reported in children with heart disease taking prescribed doses of amphetamines, including Adderall and Adderall XR. These latest reports of SUD have been in children without structural heart disease who were taking the drugs as prescribed. The FDA is looking at these reports, but “does not feel that any immediate changes are warranted in the FDA labeling or approved use of this drug.” More information is available on the FDA web site at FDA.gov.