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## INSIDE



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*Clinical Oncology Alert*'s Editor, William Ershler, MD, is on the speaker's bureau for Wyeth and does research for Ortho Biotech. Peer reviewer V.R. Veerapalli, MD, reports no financial relationship to this field of study.

# HER-2 Neu Overexpression in Older Women with Breast Cancer

ABSTRACT & COMMENTARY

***By William B. Ershler, MD, Editor***

***Synopsis:*** *In a retrospective review of data from 153 breast cancer patients 70 years and older who were treated with wide local excision and irradiation for early stage breast cancer, Her-2 neu overexpression was shown to predict axillary nodal involvement and be associated with nodal and distant failure and reduced cause-specific survival. Her-2 neu may prove a useful biomarker for decisions regarding which elderly patients will benefit from more aggressive management.*

**Source:** Poltinnikov IM, et al. Impact of Her-2 neu overexpression on outcome of elderly women treated with wide local excision and breast irradiation for early stage breast cancer: An exploratory analysis. *Am J Clin Oncol.* 2006;29:71-79.

Optimal treatment for older patients with breast cancer remains controversial and investigation in this regard is imperative as we acknowledge the median age for breast cancer is approximately 70 years and consider the population demography which indicates a shift towards older age. Without sufficient data to direct otherwise, breast cancer management in the elderly typically remains less aggressive. For example, surgical evaluation of the axilla is more often omitted and chemotherapy is less frequently prescribed, particularly in the adjuvant setting. It would be inappropriate to criticize the practicing oncologist for this because most are aware that elderly patients are less frequently included in clinical trials, and those who are included may not be representative of the typical breast cancer patient in their age group. Thus, there is yet to be established guidelines for the treatment of 'typical' older breast cancer patients, particularly those with existing comorbidities and/or functional impairments.

Poltinnikov and colleagues at the Kimmel Cancer Center of Jefferson Medical College (Philadelphia) have performed a retrospective analysis of elderly (> 70 years) women with stage I-II breast

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cancer who were managed with wide local excision and breast irradiation. The purpose of their retrospective review was to determine the clinical importance of over-expression of Her-2 neu with regard to disease recurrence and overall survival in this population. Of the 153 patients who met age and stage criteria, Her-2 neu data was available for 106; 22% of whom were Her-2 neu positive and 78% negative. Her-2 neu positivity was significantly associated with high histological grade ($P$ = 0.008), T2 stage ($P$ = 0.001) and positive axillary lymph nodes ($P$ = 0.02) among 73 patients who had surgical assessment of axilla. Overall, only 15 patients (14%) received chemotherapy. There were no recurrences in the breast. Her-2 positivity predicted for nodal and distant failure (NDF) and cause-specific survival (CSS). Projected 5-year freedom from NDF was 70% for Her-2 neu positive and 97% for Her-2 neu negative patients. CSS was 86% for Her-2 neu positive and 98% for Her-2 negative patients ($P$ < 0.01). Overall survival was no different between Her-2 neu positive and Her-2 negative patients (80% vs 85%). Thus, similar to the trend in younger patients, Her-2 neu positivity confers clinically more aggressive disease.

## COMMENTARY

There is a commonly held notion that breast cancer in older women is less aggressive, and this may enter the practicing oncologist's mind when developing treatment strategies, particularly for those older women who present with early stage disease. Yet, an emerging literature, primarily retrospective analyses, demonstrates that under-treatment, such as omission of surgical evaluation of the axilla and elimination of adjuvant radiation and chemotherapy, strongly decreases prognosis of elderly breast cancer patients.[1-3] However, for the practitioner confronted with an older patient, other factors must also be considered, including comorbidities and functional impairments which are both more frequent with advancing age.[4] As we gather data on older patients with breast cancer it is important to note similarities and differences with regard to tumor biology and predicted clinical course as they occur in younger patients.

The current retrospective analysis is illustrative. In their series of elderly women who had breast conserving primary management, most patients (69%) had surgical evaluation of the axilla as well and 23% (17/73) were found to have evidence of carcinoma in the axillary nodes. For those whose primary tumor was Her-2 neu positive, there was a significant increased risk of axillary node positivity. Furthermore, Her-2 neu positivity conferred a higher rate of nodal and distant failure and a worse cause-specific failure.

Oncologists faced with a decision whether or not to treat older women with breast cancer after excision and axillary node dissection may refer to data from prospective trials (most of which included a non-representative sample of older patients), for which computer models are now available (eg, www.adjuvantonline.com) that predict risk of relapse and death from breast cancer based upon patient's age, primary tumor size, histological grade and ER status. To the extent that this data is derived from those older patients who are otherwise 'fit' enough to meet trial entry criteria, there should be caution regarding extrapolation to the typical elderly patient. In this regard, biological markers of disease aggressiveness, such as the over expression of Her-2 neu (not yet included in available computer models) should be taken into consideration.

As with just about every clinical paradigm in medical oncology, the field awaits prospective trials to guide decision making with regard to typical geriatric cancer patients, including those with comorbidities and functional impairments. In the meantime, this report would indicate that those older women with primary tumors that overexpress Her-2 neu should not be considered to have indolent disease, and these individuals are among those that will more likely benefit from more aggressive management. ■

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# 3-Drug Treatment for Transitional Cell Carcinoma: Determining Dose and Schedule

***By William B. Ershler, MD, Editor***

ABSTRACT & COMMENTARY

***Synopsis:*** *Transitional cell carcinoma remains a fairly prevalent disease and, when locally advanced, or metastatic, effective drug combinations have been useful. However, these combinations have been quite toxic and also approximately 50% of patients do not respond. In the current trial, three drugs (cisplatin, gemcitabine and docetaxel) are investigated at two dose levels. The, lower dose level, although associated with some toxicity, was shown to have significant antitumor activity for the majority of patients. The dose and schedule presented seems reasonable to be forwarded as recommended for phase II and III investigation.*

**Source:** Tinker A, et al. A phase I dose finding study of cisplatin, gemcitabine, and weekly docetaxel for patients with advanced transitional cell cancer. *Am J Clin Oncol.* 2006;29:3-7.

THE AIM OF THIS STUDY WAS TO DETERMINE THE toxicity of a 3-drug regimen (cisplatin, gemcitabine, and docetaxel) for patients with advanced transitional cell carcinoma. To this end, Tinker and colleagues report the results from a phase I trial in which 13 patients were enrolled. The first 3 were treated at one dose level (cisplatin 70 mg/m$^2$ on day 1; gemcitabine 1000 mg/m$^3$ days 1 and 8; and docetaxel 30 mg/m$^2$ days 1 and 8 every 21 days) and when dose limiting toxicity occurred the subsequent 10 received a lower dose of one of the drugs (gemcitabine 800 mg/m$^2$ on days 1 and 8) with the doses of cisplatin (70 mg/m$^2$ on day 1) and docetaxel (30 mg/m$^2$ days 1 and 8) were maintained. The order of chemotherapy administration was docetaxel followed by gemcitabine and then cisplatin. Docetaxel and gemcitabine were administered over 30 minutes and cisplatin was administered over 1 hour with hydration. The plan was to enroll 3 patients at each dose level and the dose limiting toxicity (DLT) was defined as any grade 3 or 4 nonhematologic toxicity (except nausea or vomiting) or hematologic toxicity defined as any grade 4 thrombocytopenia, or neutropenia defined as grade 4 toxicity lasting > 5 days in total duration or febrile neutropenia. If 1 patient at a dose level experienced DLT, additional patients were entered at that level to a planned maximum of 6 patients. If 2 patients experienced DLT, then accrual stopped at that level, with the next lower dose level declared the maximum tolerable dose (MTD). It was planned to add additional patients at the MTD to reach 10 patients. Objective response was evaluated after every second cycle.

At the first dose level, one of three patients experienced hematologic DLT (febrile neutropenia) and 2 experience non hematologic DLT (grade 3 diarrhea). At the lower dose level, 1 (of 10) patients experienced febrile neutropenia and 1 had grade 3 diarrhea. Hematologic toxicity at the lower dose included 2 (of 10) with grade 3 and 4 (of 10) with grade 4 neutropenia. Three patients developed grade 3 and 1 developed grade 4 thrombocytopenia. Most nonhematologic toxicity was mild or moderate. The most common toxicity was fatigue, reported in 10 of 13 patients.

Of the 13 patients, 11 received a minimum of two cycles and were thus evaluable for treatment response. At the initial dose level, 2 (of 3) patients achieved a complete response (CR) and at the lower dose level 1 patient achieved CR, 5 patients had PR and 3 had stabilization of disease. Thus, for all evaluated patients, 8 out of 11 had a confirmed response. The median duration of response, measured from the first day of treatment until date of last follow-up, or to first evidence of disease progression was 10.3 months. AT the time of publication, eight patients were alive and median survival had not been reached.

## COMMENTARY

The trial was designed as an open label, multicenter, nonrandomized phase I dose finding study of gemc-

itabine and cisplatin with weekly docetaxel on a 21 day schedule in patients with advanced transitional cell carcinoma (TCC). Currently, the standard chemotherapy approach is a combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) which has produced response rates of 40-50%[1] but is associated with considerable toxicity (mucositis and neutropenia).[2] Docetaxel and gemcitabine have single-agent activity and when combined with platinum analogues (cisplatin or carboplatin) response rates have been as high as 60% and with less toxicity.[3-5] Thus, a strategy has been proposed to use the triplet (cisplatin, gemcitabine and docetaxel) as first line metastatic TCC treatment to improve overall response rate and survival. The drugs, however, have some overlapping toxicities and a dose finding trial, prior to phase II and III investigations was warranted.

This brief report is notable for several reasons. Among these are that the research achieved its goal of defining a reasonable dose and schedule for future investigation. The three drug combination seems a reasonable approach to realizing a more effective treatment for metastatic or locally-advanced TCC. However, it remains to be seen whether this provides advantage over doublets of cisplatin with either gemcitabine or docetaxel.

Additionally, the paper is a fine example of well articulated clinical trial methodology. This was a well conceived and designed investigation and the results were clearly presented. The paper is a fine example for those interested in the design of clinical trials and would be a useful, in this regard for medical oncology fellows and others who are learning the nuances of drug development and combination chemotherapy. ■

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# Therapy for Elderly Multiple Myeloma Patients

ABSTRACT & COMMENTARY


***By Andrew S. Artz, MD***

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*Dr. Artz reports no financial relationship to this field of study.*



***Synopsis:*** *This large European randomized trial of elderly MM patients helps delineate the role of initial therapy for elderly patients not considered eligible for autologous stem cell transplant. There were 488 eligible patients 65 to 75 years of age randomized to melphalan-prednisone (MP), dexamethasone (DEX) alone, M-DEX, or DEX-interferon-alfa 2b (DEX-IFN). Complete responses were rare. More patients in the M-DEX achieved a PR than in the other arms. PFS survival was superior in the MP and M-DEX arms but OS was similar. MP had the least non-hematologic toxicity. In elderly MM patients not eligible for transplant, MP remains the standard approach as initial therapy. The benefit of novel agents in this population requires testing.*


**Source:** Facon T, et al. Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. *Blood*. 2006;107: 1292-1298.

High-dose myeloablative chemotherapy followed by autologous stem cell rescue has been the standard therapy for eligible patients with multiple myeloma (MM)[1], although the timing of transplant remains controversial. Melphalan-Prednisone (MP) is often considered for those ineligible for transplant and has been standard for over 30 years. High dose pulse dexamethasone (DEX) monotherapy has often been employed as it accounts for the majority of the activity of VAD (vincristine, adriamycin, dexamethasone) but is better tolerated.[2]

Between 1995 and 1998, the Intergroupe Francophone du Myelome (IFM) group randomized newly diagnosed

MM patients aged 65 to 75 years requiring treatment to MP vs 3 other Dexamethasone-based regimens: M-DEX (melphalan-dexamethasone), DEX alone, and DEX-IFN (DEX-interferon alfa-2b). The median age was 70 years for the 488 eligible patients who were equally allocated among the four treatment groups. The data safety and monitoring board stopped accrual based upon on an interim analysis. Compared to MP and M-DEX, DEX showed inferior PFS ($P < 0.001$) and OS ($P = 0.03$).

Complete responses were rare. At least a PR was obtained by 70% in the M-DEX arm compared to approximately 40% in the other 3 arms ($P < 0.001$). The melphalan groups (MP and M-DEX) had significantly longer PFS (22.4 ± 1.2 months) than the DEX and DEX-IFN groups vs (12.6 ± 1.3 months) (RR, 1.55; $P < .001$). Overall survival did not differ among groups. Severe non-hematologic toxicities were lower in MP (16%) compared to the DEX based regimens (28%) ($P = .01$).

## COMMENTARY

While high-dose chemotherapy followed by autologous stem cell transplantation remains the standard approach for younger patients with MM, the majority of patients are older and may not necessarily be eligible or benefit from such an approach. Trials guiding treatment in this large cohort have been limited.

This large scale randomized trial comparing MP to three other DEX based regimens of DEX alone, Melphalan-DEX, and DEX-interferon alfa-2b offers guidance. Melphalan-based regimens (MP, M-DEX) showed improved PFS. No OS benefit was demonstrated although the study was stopped early by the data safety and monitoring board. The enhanced response rate of M-DEX was counterbalanced by the increased non-hematologic toxicities of the DEX based regimens compared to MP. The authors appropriately conclude the MP is a reasonable standard therapy for elderly patients ineligible for transplant. Those needing a more rapid response may be considered for DEX alone or M-DEX initially. One drawback to initial MP therapy however is the myelotoxicity of melphalan may prevent eventual autologous stem cell collection should the patient later be considered transplant eligible.

The low complete response rates in initial therapy of all the tested combinations suggest a potential role for newer agents with significant activity such as thalidomide, bortezomib, or lenalidomide. Such agents require testing as initial therapy in older MM patient with a watchful eye on both response rates and toxicity.

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# Does Aggressive Surgery Only Benefit Patients with Less Advanced Ovarian Cancer?

ABSTRACT & COMMENTARY


***By Robert L. Coleman, MD***

*Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston*

*Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.*



***Synopsis:*** *Increased PFS associated with optimal surgery is limited to patients with less advanced disease, arguing for case selection rather than aggressive debulking in all patients irrespective of disease extent. Lymphadenectomy may have beneficial effects on PFS in optimally debulked patients.*



**Source:** Crawford SC, et al. Does Aggressive Surgery Only Benefit Patients With Less Advanced Ovarian Cancer? Results From an International Comparison Within the SCOTROC-1 Trial. J Clin Oncol. 2005;23:8802-8811.


The positive relationship between the amount of surgical residual following primary extirpation of advanced ovarian cancer and survival thereafter has been one frequently cited to justify aggressive surgical evaluation. This bias was initially suggested 3 decades ago and although it has never been proven by a randomized trial, several retrospective, prospective and meta-analyses of clinical trials appear to support the contention. Crawford and colleagues, applying the results from a recently reported randomized controlled clinical trial of post-operative chemotherapy, evaluated this question across a large cohort of ovarian cancer patients with stage IC to IV disease.

The cohorts consisted of 1077 women enrolled in the Scottish Randomized Trial in Ovarian Cancer (SCOTROC-1) trial and randomized to receive combination paclitaxel and carboplatin or docetaxel and carboplatin following surgery. Women were recruited from centers both within the United Kingdom (UK) and out-

side the UK. The trial was powered to address a 25% improvement in the median progression-free survival (PFS) for the docetaxel/carboplatin combination. The primary end point, reported previously, demonstrated that median PFS would not be different between the cohorts; thus, it has been widely interpreted that the 2 regimens are equivalent. The primary aim of the current study was to evaluate PFS by surgical outcome, in particular, among patients recruited from within and outside the UK. The premise for this division was based on an observation that less aggressive surgery might be occurring within the UK centers, explaining the disparate survival results observed in these sites compared to other European countries. Three main observations were noted: first, compared to non-UK centers, patients treated within the participating UK sites were significantly less likely to be optimally debulked (≤ 2 cm residual). Second, optimal cytoreduction was associated with an increased PFS; however, the effect was greatest among the patients with less extensive disease at presentation. And third, patients treated within UK sites and with no visible residual disease had a poorer survival than similar residua patients treated outside the UK. This latter observation appeared to be related to the performance of retroperitoneal lymphadenectomy. Crawford et al concluded that the increase in PFS with optimal cytoreduction is limited to patients with less advanced disease at presentation and likely reflects underlying characteristics of tumor biology and that lymphadenectomy may have beneficial effects on PFS in patients without disease residual.

## COMMENTARY

The mantra to be aggressive surgically in newly diagnosed advanced staged ovarian cancer patients is a majority consensus throughout the United States and much of the world. Several factors have supported this strategy. First, there are several data sets in the literature that appear to document better outcomes in patients left postoperatively with less residual disease. "Optimal" has been variably defined over the years (by convention it is usually referred to as no individual nodule larger than 1 cm in greatest dimension) but it is hard to accurately estimate. While many have documented that inherent biology may dictate which patients are "debulkable," others have argued that surgical aggressiveness can even overcome this characteristic. Even patients with parenchymal stage IV disease (eg, hepatic metastases) appear to benefit from an aggressive intraperitoneal resection compared to those who are left with bulky intraperitoneal disease. Crawford et al strongly advocate primary surgery for all newly diagnosed patients.

Second, despite the lack of randomized clinical trials, very large data sets subjected to meta-analysis document a near linear relationship between the degree of cytoreduction and survival. However, when studying a cohort of patients deemed "optimal," there is wide variation in survival depending on the amount of disease present before attempting cytoreduction. Third, there is a concern that not operating when the diagnosis has been suspected may select a higher proportion of resistant cells ultimately reducing survival. This argument has been advanced against the use of neoadjuvant chemotherapy in patients with advanced disease at presentation.

Fortunately, this issue is being studied in a randomized clinical trial, which should shed light in this contentious area. And fourth, based a recent randomized clinical trial documenting the merits of retroperitoneal lymphadenectomy on PFS, many authors are now advocating systematic surgical evaluation in all patients with advanced disease but particularly in those deemed optimal.[1-3]

Circumstantial evidence abounds, and the current trial appears to fuel the fire. However, there are important nuances brought to light by the SCOTROC-1 trial that have bearing on our enthusiasm for taking an aggressive position. Biology may be important after all. In the current trial, only those patients in the first two quartiles of initial disease volume appeared to benefit from optimal surgery. Currently, studies evaluating the genetic and proteomic signature of patients are underway and preliminarily appear to identify several factors which, if validated, could be used to identify those patients in whom an aggressive surgical attempt should be made and those who are unlikely to benefit from such a procedure. In addition, attention again is directed to the retroperitoneum as a potential haven for metastatic disease. Given the ability to evaluate this area in most patients undergoing surgical extirpation, it is reasonable to add this procedure to those cytoreduced to no visible or minimal visible disease. While a randomized trial would provide the statistical proof necessary to satisfy all in this debate, studies like the current one help to refine the process of providing the appropriate surgery for the appropriate patient with advance ovarian cancer. ■

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# The Gaining Prominence of Chemotherapy in the Adjuvant Treatment of Advanced Endometrial Cancer

ABSTRACT & COMMENTARY

***By Robert L. Coleman, MD***

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*Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.*

***Synopsis:*** *Chemotherapy with doxorubicin-cisplatin significantly improved progression-free and overall survival compared with WAI. Nevertheless, further advances in efficacy and reduction in toxicity are clearly needed.*

**Source:** Randall M, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2006;24: 36-44.

Advanced stage endometrial cancer represents a significant therapeutic challenge as it encompasses patients with a diverse spectrum of disease and recurrence risk. Currently, most patients are treated following primary surgical extirpation with a modality either directed at tumor residua or to a high-risk locale of recurrence. Either or both radiation therapy and chemotherapy have been used. Both have been considered to be feasible and effective. Randall and colleagues addressed the question as to which was better in a randomized clinical trial of whole abdominal irradiation (WAI) vs combination chemotherapy with cisplatin and doxorubicin. Nearly 400 patients were entered over 8 years. Patients with stage III or IV (≤ 2 cm post-operative residual) disease were eligible. Both groups were well balanced for known prognostic factors including percent of stage III vs IV disease, nodal status, age, and performance status.

Overall, more patients completed WAI than chemotherapy and experienced less systemic toxicity. Treatment-related deaths, however, were similar on both arms. Progression-free and overall survival were significantly improved with chemotherapy relative to WAI. The reduction in the risk for progression for patients treated with chemotherapy was 33% and for overall survival, 31%; both are highly statistically significant. Subgroup analysis demonstrated that the benefit estimates were similar when evaluated by stage (III vs IV). The authors concluded that cisplatin and doxorubicin chemotherapy significantly improved progression-free and overall survival compared to WAI. However, significant modality-related toxicity should prompt investigation of alternative regimens.

## COMMENTARY

Endometrial cancer is the most frequently diagnosed gynecologic malignancy in the United States. Fortunately, most patients have organ-confined disease, which is highly curable with surgery with or without adjuvant therapy. However, patients with more advanced disease comprise the majority of disease-related deaths associated with this condition. Strategies to treat these patients have largely been directed to the known disease (eg, node-bearing tissues) or to the likely patterns of recurrence (eg, vaginal cuff or intra-abdominal locations). This has led to a diverse set of treatment recommendations and a diverse set of reported outcomes in uncontrolled clinical trials.[1-3] Another challenge in this setting is the higher representation of high-grade and atypical histologies, such as clear cell and serous, which have a somewhat different natural history. Thus, a review of the literature comprising patients classified as "advanced stage" leaves the reader with a confusing picture of treatment recommendations and expectations.

Traditionally, it has been felt that advanced stage endometrial cancer patients represent a cohort with a significant risk of local and regional disease recurrence. This has been particularly true of patients with known metastatic disease in the abdomen (Stage IV). Those patients with small volume residual disease following surgery have been approached with WAI with significant survival characteristics. Given that patients may recur distantly with similar probabilities, attention has recently turned to the evaluation of systemic chemotherapy. The current trial represents the first such completed trial comparing the modalities head to head. It was somewhat of a surprise that chemotherapy performed as well as it did. Despite being more toxic and less likely to be completed in full, it signifi-

cantly reduced the risk of disease progression and death by almost one-third. The results held true even in cases where radiation is considered a favored modality given its long track record of success and the oft-considered chemotherapy-sanctuary of the retroperitoneal lymphatics. To be fair, it is likely that WAI is not the best form of radiotherapy to administer in this setting, particularly in patients with stage III disease or in patients with 2 cm macroscopic residual tumors. Better case selection may have offered a more balanced trial. However, these results have ushered in an intensive investigation portfolio of expanded chemotherapy use and novel treatment packages utilizing radiation and chemotherapy for similarly staged patients. The report represents a significant contribution to the literature and is a tribute to the Gynecologic Oncology Group's investigator's tenacity to complete a difficult trial of divergent methodologies. ■

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## CME Questions

**6. Which therapy had the fewest patients suffering severe non-hematologic toxicity?**
a. Melphalan-Prednisone (MP)
b. Dexamethasone alone (DEX)
c. Melphalan-Dexamethasone (M-DEX)
d. Dexamethasone and interferon alfa-2b (DEX-IFN)

**7. In the report by Tinker and colleagues, the most prevalent reported toxicity among the ten patients at the reduced dose level was:**
a. neutropenia
b. anemia
c. constipation
d. fatigue

**8. Among elderly patients with primary breast cancers that overexpress Her-2 neu, the data from Poltinnikov and colleagues would indicate:**
a. a higher rate of axillary node involvement
b. an increased risk for nodal and distant failure (recurrence)
c. a reduced cause-specific survival
d. All of the above

**Answers:** 6 (a); 7 (d); 8 (d)



## CME Objectives

The objectives of *Clinical Oncology Alert* are:
- to present the latest information regarding diagnosis and treatment of various types of cancer;
- to present prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
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# Treating Opioid-Dependent Patients with OAT

A Perspective article in the Jan. 17 *Annals of Internal Medicine* reviews pain management in patients with a history of opioid addiction who are receiving opioid agonist therapy (OAT) with maintenance methadone or buprenorphine. These patients present unique challenges that frequently result in suboptimal treatment of acute pain.

The authors provide an excellent review of these challenging patients and point our 4 common misconceptions: 1) Maintenance opioids provide analgesia—not only is this not the case, but OAT may reduce the effectiveness of standard pain relief measures; 2) Opioids for analgesia may result in addiction relapse—there is no evidence that treatment of acute pain triggers relapse; 3) The additive effects of opioid analgesics and OAT may cause respiratory and CNS depression—tolerance to the respiratory and CNS effects of opioids develops rapidly and is not exacerbated by acute therapy; 4) Reporting pain is drug-seeking behavior—as long as there is clinical evidence of pain, or an acute injury, pain may be safely treated. Drug seeking and manipulation is more likely characterized by vague reports of long-term pain than requests for short term pain relief. Plus, patients on OAT are less likely to experience euphoria associated with coadministered opioids, so there is less incentive to drug seek.

The authors provide specific pain treatment recommendations for patients on methadone and buprenorphine. They conclude, "Addiction elicits neurophysiologic, behavioral, and social responses that worsen the pain experience and complicate provision of adequate analgesia. These complexities are heightened for patients with opioid dependency who are receiving OAT, for whom the neural responses of tolerance or hyperalgesia may alter the pain experience. As a consequence, opioid analgesics are less effective; higher doses administered at shortened intervals are required. Opioid agonist therapy provides little, if any, analgesia for acute pain. Fears that opioid analgesia will cause addiction relapse or respiratory and CNS depression are unfounded. Furthermore, clinicians should not allow concerns about being manipulated to cloud good clinical assessment or judgment about the patient's need for pain medications. Reassurance regarding uninterrupted OAT and aggressive pain management will mitigate anxiety and facilitate successful treatment of pain in patients receiving OAT" (Alford DP, et al. *Ann Intern Med*. 2006;144:127-134).

### *Long-Term Effects of Warfarin Use*

Warfarin use may be associated with osteoporosis and fractures in men, but not women, with atrial fibrillation, according to new study. In a retrospective cohort study of Medicare benefici-

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aries with atrial fibrillation in United States, 4461 patients on long-term warfarin therapy were compared to 7587 patients who were not prescribed warfarin. The adjusted odds ratio of fracture was 1.25 in patients who took warfarin (95% CI, 1.06-1.48). The odds ratio for men was 1.63, and a nonsignificant 1.05 for women. In patients who were prescribed warfarin for less than one year, the risk of osteoporotic fracture was not increased significantly. The authors speculate that since warfarin blocks vitamin K dependent clotting factors, it may also block vitamin K dependent osteocalcin and other bone matrix proteins. Interestingly, use of beta blockers reduced the risk of fracture in this population. The authors conclude that long-term use of warfarin was associated with osteoporotic fractures in men with atrial fibrillation, and that beta-blockers may be somewhat protective (Gage BF, et al. *Arch Intern Med*. 2006;166:241-246).

## Statins' Multiple Benefits

Mounting evidence suggest that statins have benefits beyond their ability to lower LDL cholesterol. Multiple studies show that statins reduce inflammation in patients without heart failure. Now, 2 new studies suggest that they also reduce inflammation in patients with heart failure. In a study from Emory University, 108 patients with nonischemic heart failure were randomized to atorvastatin 20 mg per day or placebo. Inflammatory markers such as C reactive protein, interleukin-6, and TNF-alpha were all reduced in the atorvastatin group. Atorvastatin treated patients also showed an improvement in LVEF from 0.33-0.37 over one year ($P$ = 0.01) (Sola S, et al. *J Am Coll Cardiol*. 2006;47:332-337).

A second study, from Harvard, in patients with heart failure showed that atorvastatin 10 mg/ day led to an 8% reduction in TNF receptor 1, a 37% reduction in C reactive protein, and a 17% reduction in endothelin-1 (Mozaffarian D, et al. *Am J Cardiol*. 2005;96:1699-1704). Atorvastatin may also have anti-thrombotic effects in patients with unstable angina according to a study from Greece. Forty-five patients with normal cholesterol levels and unstable angina were randomized to 10 mg of atorvastatin or placebo, starting right after hospital admission and continuing for 6 weeks. After one week of treatment circulating levels of anti-thrombin III, factor V, and von Willebrand factor were all significantly reduced in the atorvastatin group (Tousoulis D, et al. *Int J Cardiol*. 2006;106:333-337).

## FDA Actions

The FDA has approved the first inhaled insulin for the treatment of adults with type I and type 2 diabetes. Inhaled insulin, a powder form of recombinant human insulin, has been in development for over 10 years, and has been the subject of intense scrutiny by the FDA. Concerns over long-term safety, particularly in people with underlying lung disease, has delayed approval, and safety in children and teenagers is still under investigation. Inhaled insulin is delivered through a device that is significantly larger than an asthma inhaler and, even folded, is the size of a flashlight. A blister pack of insulin powder is inserted into the device, which is then triggered. It is not to be used by smokers or people who quit smoking within last 6 months, and is not recommended for people with asthma, bronchitis, or emphysema. The FDA also recommends pulmonary function testing prior to starting inhalation therapy, and every 6 to 12 months thereafter. Although the product is approved for treatment of both type I and type 2 diabetes, fewer than 30% of type I diabetics achieve adequate control with inhaled insulin alone. Inhaled insulin is a joint effort by Pfizer, Sanofi-Aventis, and Nektar Therapeutics. It will be marketed under the trade name Exubera.

The FDA has approved an intravenous form of Ibandronate that can be administered every 3 months for the treatment of postmenopausal osteoporosis. The 3 mg dose is injected intravenously over 15 to 30 seconds by a healthcare professional. The drug is an option for women who cannot take pills or are unable to sit upright for 30 to 60 minutes after taking an oral bisphosphonate. Efficacy with the injectable form of ibandronate was better than once-a-day oral dosing of Ibandronate 2.5 mg in a study of over 1300 women with osteoporosis. Intravenous and oral forms of the drug were equally well tolerated. The FDA is recommending measurement of serum creatinines prior to administration each dose. Ibandronate is also approved is a 2.5 mg once a day oral dose and a 150 mg monthly oral dose. All 3 formulations are marketed as Boniva.

Berlex's combination estradiol-levonorgestrel patch (Climara Pro) has been approved for the indication for prevention of postmenopausal osteoporosis in women with an intact uterus. The patch was previously approved for the indication of moderate to severe vasomotor symptoms associated with menopause. The osteoporosis indication was based on a 2-year, double-blind, randomized trial that showed that the estradiol-levonorgestrel patch was associated with significant maintenance of bone density compared to placebo. ■