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Irinotecan in Metastatic Colorectal Cancer

ABSTRACT & COMMENTARY

Of the 131,600 new cases of colorectal cancer that were expected in the United States during 1998, about half were curable with surgery or surgery plus adjuvant chemotherapy. In addition, adjuvant radiation therapy plays a role in the local control of rectal, but not colon primaries. However, the other half either present with or will develop metastatic disease. Primary therapy of metastatic colorectal cancer most often includes 5-fluorouracil plus folinic acid, but the doses and schedule of administration vary. No consensus has developed regarding the treatment of metastatic colorectal cancer that fails to respond to or progresses after first-line 5-fluorouracil-based therapy. In phase II studies, at least two agents have shown promising response rates in the setting of 5-fluorouracil-resistant disease: oxaloplatin[1] and irinotecan.[2,3] Irinotecan has recently been tested in two prospective randomized studies against infusional 5-fluorouracil in one and against best supportive care in another.

Rougier and colleagues randomly assigned 133 patients to irinotecan 300-350 mg/m^2 by 90-minute infusion every three weeks and 134 patients to 5-fluorouracil given by one of three standard continuous infusion protocols (regimen 1-folinic acid 200 mg/m^2 over 2 h followed by 400 mg/m^2 5-fluorouracil by IV bolus, then 600 mg/m^2/d continuous infusion for 2 days every 2 weeks; regimen 2-5-fluorouracil 250-300 mg/m^2/d continuously until progression or toxicity; regimen 3-5-fluorouracil 2.6-3 g/m^2/d for 24 hours with or without folinic acid 20-500 mg/m^2 intravenously per day weekly for 6 weeks with 2-week rest periods between cycles). All patients had received first-line therapy with a 5-fluorouracil regimen and had either failed to respond or had progressive disease on therapy. Treatment with irinotecan or infusional 5-fluorouracil was given until disease progression, unacceptable toxicity, or patient refusal of further treatment. Overall survival was the primary end point, but progression-free survival, response rate, symptom-free survival, and quality of life were also assessed.

Patients treated with irinotecan lived significantly longer than those treated with infusional 5-fluorouracil. One-year survival was 45% among irinotecan-treated patients and 32% for 5-fluorouracil-treated patients (P = 0.035). Median survival was 10.8 months for

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the irinotecan group and 8.5 months for the 5-fluorouracil group. Median progression-free survival was 4.2 months with irinotecan and 2.9 months with 5-fluorouracil (P = 0.03). Median pain-free survival favored irinotecan, but not significantly. Toxicities were quantitatively similar on the two arms and quality-of-life assessments were comparable.

Cunningham and colleagues randomly assigned patients to irinotecan or to best supportive care in a 2:1 randomization; thus, 189 patients received irinotecan in the same dose and schedule as the Rougier et al study and 90 patients received symptomatic supportive care. Overall survival was significantly better in the irinotecan group—36.2% one-year survival vs. 13.8% one-year survival with best supportive care (P = 0.0001). Survival without weight loss, without pain, and without performance status deterioration were all significantly improved on the irinotecan arm. Diarrhea, a known dose-limiting toxicity from irinotecan, was the only symptom that was worse on irinotecan. All other significant differences in quality of life measures between the groups favored irinotecan.

Thus, these two prospective randomized clinical trials appear to establish irinotecan as a consensus choice for second-line therapy of metastatic colorectal cancer. (Rougier P, et al. *Lancet* 1998;352:1407-1412; Cunningham D, et al. *Lancet* 1998;352:1413-1418.)

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COMMENTARY

Irinotecan (also known as CPT-11) is a topoisomerase I inhibitor. Topoisomerase I is involved in the relaxation of supercoiled DNA. The enzyme cleaves one strand of the DNA and permits the double helix adjacent to the cut to unwind and then it reseals the single-stranded break. The inhibitors bind to the enzyme that is bound to DNA and interfere with the religation of the single-strand break. Thus, the enzyme results in the accumulation of single-strand DNA breaks. However, it is not completely clear how the topoisomerase I inhibitors ultimately kill the cell.

Irinotecan has two dose-limiting toxicities—myelosuppression (mainly neutropenia) and diarrhea. The diarrhea seems to be related to the concentration of SN-38, an active metabolite, converted in the intestine upon hepatic clearance and excretion of the drug. The diarrhea is of two types: one acute syndrome occurring within an hour after completing the infusion and the other delayed, occurring more than 12 hours after infusion and usually after the second or third weekly dose. The first or acute form is rarely dose limiting. The second form can be serious. High doses of loperamide are useful in controlling the diarrhea in most cases (4 mg initial dose followed by 2 mg every 2 hours or 4 mg every 4 hours until diarrhea has stopped for at least 12 hours); furthermore, octreotide also appears to be effective.

These clinical trials establish irinotecan as a standard second-line treatment for patients with metastatic colorectal cancer. These results somewhat complicate matters for those interested in drug development in colorectal cancer. In the first place, new drugs will be tested later in the course of the disease from now on. Only patients who have progressed on 5-fluorouracil and irinotecan will enter phase II studies of new agents. Furthermore, if phase II trials look promising, the next step is a phase III salvage study because it will now be necessary to compare every new active agent to irinotecan in patients who have progressed on 5-fluorouracil. This progress in treatment is slowing subsequent progress, which is not a happy outcome from these studies.

The magnitude of the survival advantage seen with irinotecan in these studies is small—2.3 months in one study and 2.7 months in the other. The influence of the drug on one-year survival was 13% in one study and 22.4% in the other. Thus, many patients are treated to extend the lives of a few. Although adjuvant therapy is similar in its "many are called, few are chosen" features, at least adjuvant therapy does not typically have a major adverse effect on quality of life. The diarrhea from irinotecan does have the potential to adversely affect quality of life. However, even in patients whose survival was not improved by the treatment, quality of life end

points would seem to favor irinotecan as well.

Other agents of interest in colorectal cancer include oxaliplatin and capecitabine. Despite a long history of disappointment with "rational" drug combinations, it is at least possible that an empiric combination will improve upon single agent results. Although the progess is slow and incremental, it feels like solid tumors are finally beginning to respond to our newer therapies a bit more. And, with the apparent enhancement in antitumor effects being seen with antibodies plus chemotherapy in lymphoma and breast cancer, it may be that authentic progress in the treatment of common solid tumors is on the horizon. ❖

References

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2. Van Cutsem E, et al. *Proc Am Soc Clin Oncol* 1997; 16:268a.
3. Rougier P, et al. *J Clin Oncol* 1997;15:251-260.

Irinotecan is a topoisomerase I inhibitor that has activity in colorectal carcinoma. Which of the following statements about irinotecan is true?

a. Irinotecan plus 5-fluorouracil is more effective than 5-fluorouracil alone in the primary treatment of metastatic colorectal cancer.
b. Irinotecan is the treatment of choice for adjuvant therapy of stage B colorectal carcinoma.
c. Irinotecan is more effective than folinic acid at modulating the antitumor effects of 5-fluorouracil.
d. Irinotecan is more effective than infusional 5-fluorouracil or best supportive care in the second-line treatment of metastatic colorectal cancer.

Epoetin Alfa and Improved Quality of Life for Anemic Cancer Patients

ABSTRACT & COMMENTARY

Synopsis: *Previous studies have reported improved quality of life in cancer patients treated with recombinant erythropoietin, presumably on the basis of increased hemoglobin and tissue oxygen delivery. However, these studies had not accounted for the possible role that response to chemotherapy had in achieving the observed increased well being.*

Source: Demetri GD, et al. *J Clin Oncol* 1998;16: 3412-3425.

A large, multicenter, community-based study was undertaken to prospectively assess the effectiveness of erythropoietin (epoetin alfa) as an adjunct to chemotherapy in patients with cancer and anemia based upon changes in quality of life parameters and hemoglobin levels and to correlate these changes with antitumor response. Two thousand three hundred patients with nonmyeloid malignancies who received chemotherapy were enrolled in this study from 621 U.S. community-based practices. Patients received epoetin alfa 10,000 U three times weekly and the dose was increased up to 20,000 U three times weekly depending on the hemoglobin response. Treatment continued for a maximum of 16 weeks in patients who showed evidence of hematological response.

Patients enrolled in the study had a wide range of malignancies and received varying chemotherapy regimens. Lung cancer accounted for 24% of the cases, breast cancer 17%, gynecologic malignancy 13%, and gastrointestinal malignancy 9%; 22% had miscellaneous malignancies. About 44% of patients did not complete the study; reasons for not completing treatment included death (10%), failure to have a rise in hemoglobin of more than 1 g/dL (7%), intercurrent illness (6%), lost to follow-up (6%), or other factors. Only 2% had an adverse response to the epoetin alfa.

Approximately 70% of patients achieved a hematological response (rise in hemoglobin of > 2 g/dL or reaching a level of 12 g/dL), and transfusion requirements were observed to be decreased for the group as a whole, but especially for those that responded.

Quality of life measures correlated significantly with hemoglobin levels and were independent of tumor response. Patients evaluated their symptoms using the linear analog scale assessment, a 10 cm scale. The mean change in energy level from baseline to study end was + 11.5 mm ($P < 0.001$), activity level was + 11.1 mm ($P < 0.001$) and overall well being was + 9.8 ($P < 0.001$). Furthermore, a direct and significant correlation was shown by regression analysis between the increase in overall quality of life and the increase in hemoglobin level from baseline.

Patients who achieved a complete response, partial response, or stable disease (with the various chemotherapy regimens) but had no increase in hemoglobin level did not have a meaningful or significant increase in quality of life as measured by linear analog scale assessments. The linear analog scale assessment correlated well with the more comprehensive quality of life measure, the FACT-An (Functional Assessment of Cancer Therapy-Anemia).[3]

Thus, epoetin alfa appears to have a benefit on patient reported quality of life for those cancer patients

with anemia who are receiving chemotherapy and this seems to be independent of the response of the tumor to cancer chemotherapy.

COMMENTARY

This is the second large clinical trial published within two years on the role of epoetin alfa in cancer patients. The first was enthusiastically anticipated, but it was inconclusive because an important host variable was not reported and could not be retrieved.[1] Although hemoglobin increases were noted and transfusion requirements were less, it was not possible to determine whether the observed increased quality of life was the result of effective tumor response to chemotherapy or the increased hemoglobin level. Common sense would suggest that both would be important, but to the extent that it needed to be proven, the study was inadequate. Thus, epoetin alfa was approved by the FDA for improving hemoglobin levels and reducing transfusion requirements in patients receiving cancer chemotherapy, but not for improving quality of life.

Not to be denied, Demetri and associates went back to the drawing board and developed this second study in which tumor responses were carefully monitored and analyzed in the context of quality of life and epoetin response. The numbers of patients were large and the magnitude of the effect is hard to refute, despite the relatively large number of patients who dropped out of the study. The 70% of patients who achieved a hemoglobin response had a self-reported energy level that was greater and their overall quality of life was improved. What's more, for those who achieved a hemoglobin response, the improvement in quality of life was significant and comparable for those whose tumors responded completely to chemotherapy, those whose tumors responded partially to chemotherapy, or those who had stable disease. Patients with progressive disease despite chemotherapy did not have improved quality of life with epoetin, even if they had a significant hemoglobin response.

Like the management of pain or nausea in cancer patients, oncologists now have an approach to offer patients with the pervasive symptom of fatigue, which so often accompanies chemotherapy. For those with anemia, the response is simple. The data are clear that correction of anemia will improve energy level and sense of well being. The question of how much epoetin and how often it should be administered remains to be clarified. Perhaps once a week dosing will be as effective as three times per week as performed in this trial, but this remains to be demonstrated. The other question that remains is what is the role for epoetin in non-anemic, but fatigued cancer chemotherapy patients. Perhaps another trial is in the offing.

An equally important issue to address is the cost. It would be of interest to compare the use of epoetin with packed red blood cell transfusion to a target hemoglobin level. One wonders whether the cost and toxicities are substantially different. Fatigue in the cancer patient whose hemoglobin level is abnormal but above 8 gm/dL could also benefit from transfusion to a level of 12 gm/dL. However, transfusions are rarely given until the hemoglobin falls below 8 gm/dL. Transfusion has a high response rate. The infectious complications of transfusion are exceedingly rare. It would be of interest to know whether there are economic, toxicity, efficacy-related advantages to epoetin compared to transfusion. The comparison of epoetin to liberalized criteria for transfusion could provide useful information. Epoetin's superiority over nothing (i.e., no effort to augment hemoglobin level) may exaggerate the magnitude of the effect. Further information is also needed on the 30% of patients who do not respond. From prior work, it seems likely that at least some of the nonresponders have high endogenous levels of erythropoietin. However, others who do not respond may have anemia of chronic disease, a cytokine-mediated defect in iron reutilization. It may be cheaper to choose candidates for epoetin by measuring endogenous erythropoietin serum levels and performing serum iron studies to exclude patients less likely to respond. ❖

Reference

1. Glaspy J, et al. *J Clin Oncol* 1997;15:1218-1234.

Which of the following statements about the use of Epoetin alfa in cancer patients receiving chemotherapy is *not* true?

a. When administered three times weekly, it has been shown to improve patient reported energy level and general well being.
b. When administered three times weekly, it has been shown to improve quality of life for all patients who achieved a hemoglobin response of 2 g/dL, independent of tumor response.
c. When administered three times weekly, it has been shown to increase hemoglobin levels in approximately two of three patients and decrease transfusion requirements.
d. When administered three times weekly in patients with nonmyeloid malignancies, it has been shown to increase hemoglobin levels in patients independent of tumor type.

Timing of High-Dose Therapy For Myeloma

ABSTRACT & COMMENTARY

Synopsis: *Multiple myeloma remains an incurable illness, even with high-dose chemotherapy and autologous or allogeneic transplantation. However, high-dose ther-*

apy has definitely enhanced overall survival, extending median survival from less than three years to greater than five years in most series.

Source: Fermand JP, et al. *Blood* 1998;92:3131-3136.

The median survival for patients with multiple myeloma treated with conventional dose chemotherapy remains less than three years. However, treatment with high-dose therapy (HDT) with autologous stem cell support has been shown in a number of phase II trials to enhance survival to five years or more.[1-3] One of the many questions that remains is when is the appropriate time to use HDT? Should it be used as initial therapy or should it be reserved until a patient has become refractory to conventional chemotherapy? The French "Myelome Autograffe" group set out in 1990 to address this question. This report details that clinical investigation.

Two hundred two previously untreated myeloma patients were entered on a multicenter sequential randomized trial to assess the optimal timing of HDT and peripheral blood stem cell autotransplantation. Eligibility criteria included age younger than 56 years, symptomatic disease (not stage I by the Durie and Salmon classification), no more than one prior cycle of cytotoxic chemotherapy, and the absence of severe liver, kidney, or heart disease. Eligible patients (n = 185) were randomly assigned to receive HDT and PBSC autotransplantation (early HDT, n = 91) or a conventional-dose chemotherapy (CCT) regimen (late HDT group, n = 94). In the late HDT group, HDT and transplantation were performed as rescue treatment, in case of primary resistance to CCT or at relapse in responders. In all cases, PBSC were collected before randomization, after mobilization by chemotherapy. In both groups, HDT was preceded by three or four treatments with vincristine, doxorubicin, and methylprednisilone. Data were analyzed on an intent-to-treat basis using a sequential design.

At a median follow-up of 58 months, estimated median overall survival (OS) was 64.6 months in the early HDT group and 64 months in the late HDT group. Survival curves were not significantly different. The average time without symptoms, treatment, and treatment toxicity (TWiSTT) was 27.8 months for the early HDT group and 22.3 months for the late HDT group.

COMMENTARY

For younger patients with multiple myeloma, HDT with autologous stem cell transplant has been clearly demonstrated to provide survival advantages. There are some data suggesting that older patients would also benefit from this approach,[4] but firm conclusions are not yet possible in the older subgroup. For selected individuals, sequential HDT (i.e., two autologous transplants) may offer even greater overall survival.[5] In contrast, allogeneic transplant, which offers some theoretical advantages (including a possible graft vs. tumor effect) remains associated with unacceptable toxicity and relatively high procedure-associated deaths.[6]

This report provides useful information for the practicing oncologist. Depending upon the availability of stem cell harvesting and transplantation facilities, it appears perfectly reasonable to embark upon standard chemotherapy approaches for myeloma patients of any age. Once the patient is stable, arrangements can be made for "rescue" HDT and PBSC autotransplant. However, it should be remembered that in this study, stem cell harvest was performed in all patients before treatment. The possibility that prolonged alkylating agent therapy during the initial treatment could diminish stem cell proliferative potential and possibly even result in genetic damage resulting in leukemia cannot be overlooked. Today, in contrast to the procedures of eight years ago, the use of GM-CSF to mobilize stem cells would probably reduce the first concern, but the leukemia potential remains.

An additional argument for early HDT can be made from the quality-of-life perspective. Although the differences were modest, TWiSTT was approximately 22 weeks (5½ months) longer for those receiving early HDT. This marks a real advantage in a disease that is typically associated with poor quality of life.

Thus, HDT, early or late, is associated with a median survival of more than five years. Early transplantation may be favored because it entails less chemotherapy and less overall time with toxicity. However, clinicians should be aware that if early transplantation is not possible, HDT may still be used later when the disease has become refractory to first-line, conventional approaches, or upon relapse after initial remission. ❖

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4. Vesole D, et al. *Blood* 1994;84:535a.
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Which of the following statements about the use of high-dose therapy and peripheral blood stem cell autotransplantation is true?

a. When administered after conventional chemotherapy, overall survival is less than when used as initial therapy.
b. When administered as initial therapy, overall cure rates are approximately 30%.
c. When administered as initial therapy rather than after conventional dose-therapy failure, it provides comparable overall survival and less time without symptoms.
d. When administered as initial therapy rather than after conventional dose-therapy failure, it provides comparable overall survival but more time with symptoms.

The Treatment of High-Risk Thyroid Cancer

ABSTRACT & COMMENTARY

Synopsis: *Although the majority of thyroid cancers are well controlled with primarily surgical intervention, a substantial fraction recur and a number of patients die each year with recurrent and progressive disease. The National Thyroid Cancer Treatment Cooperative Study Registry has gathered data from 14 clinical centers that treat this disorder.*

Source: Taylor T, et al. *Ann Intern Med* 1998;129: 622-627.

The treatment of high-risk thyroid carcinoma remains controversial. Key questions include the recommended extent of initial surgery, the role of iodine-131 therapy, and whether to include external beam irradiation in the initial treatment plan. In this report, data from 14 institutions in the United States and Canada (participating centers in the National Thyroid Cancer treatment Cooperative Study Register) were analyzed. Three hundred eighty-five patients with high-risk thyroid cancer (303 with papillary carcinoma and 82 with follicular carcinoma) were followed prospectively for a mean of three-and-a-half years for clinical outcomes of death, disease progression, and disease-free survival. Variables of interest included type and extent of surgery, iodine-131 therapy, and the use of external beam irradiation.

Characteristics that rendered an individual with thyroid cancer high-risk were aged older than 45 years, tumor more than 4 cm (for papillary) or more than 1 cm (for follicular), gross extraglandular invasion, neck node metastases, or distant metastases. Patients with follicular carcinoma were also considered high risk if the tumor was multifocal or if the histology revealed poor differentiation.

A total of 1607 patients with thyroid cancer were evaluated at the participating centers and, of these, 303 with papillary carcinoma and 82 with follicular carcinoma were considered high risk. Clinical outcomes were assessed with respect to each of the clinical variables mentioned.

Surgery. Of the 300 patients with papillary carcinoma, 85% had a total or near-total thyroidectomy as initial surgery. Only 3% had sub-total thyroidectomy, 9% had lobectomy, and 5% had lumpectomy or biopsy only. Similarly, for follicular carcinoma, 71% (of a total of 80 patients) had total or near-total thyroidectomy with the remainder having less extensive surgery. The overall complication rate for surgery was approximately 14%, with the most common complications being hypothyroidism or vocal cord palsy (or both hypothyroidism and vocal cord palsy). For those with papillary carcinoma, overall mortality was less with the more aggressive surgery, but the disease-free survival was not affected. The extent of surgery did not influence survival for those with high-risk follicular carcinoma.

Radioiodine Therapy. Radioiodine (iodine-131) was given to 85% of those with high-risk papillary carcinoma, but this only slightly improved cancer-specific survival in this group (compared to those that did not receive treatment) and it did not seem to influence disease-free survival at all. In contrast, radioiodine therapy was highly effective in improving outcome in patients with follicular thyroid carcinoma. Overall survival and cancer-specific survival was significantly greater for the

79% of these patients so treated, compared to the other high-risk patients not treated with radioiodine.

External Beam Radiation. Forty-six of 248 patients (18%) with high-risk papillary or follicular thyroid carcinoma had external beam radiation to the thyroid bed. The mean dose of radiation was 46 Gy over an average of 18.5 fractions. The most common clinical feature of those receiving external beam radiation was the presence of gross residual disease after surgery and/or extrathyroid invasion, although there were a substantial number of similarly involved patients not treated with this modality. Patients with high-risk papillary carcinoma treated with external beam radiation fared less well with regard to overall mortality than those not treated. Similarly, overall and cancer-specific mortality were worse for follicular carcinoma patients treated with external beam radiation.

Thus, this study supports a role for post-operative iodine-131 therapy for patients with high-risk follicular carcinoma and to a lesser extent, papillary thyroid carcinoma, but the study raises significant concerns about the use of external beam therapy in the same group.

COMMENTARY

The value of this report is that it has a relatively large series of patients for whom systematic evaluation was prospectively addressed. However, because treatment choices were not controlled and certainly varied among the various institutions, it is difficult to be confident in any, but the most basic conclusions. Certainly, the data support the use of radioiodine in high-risk patients.

The concerns about external beam irradiation must be taken with some skepticism. Patients in this series with the most negative prognostic factors (locally invasive tumors with gross residual disease) were compared to patients less likely to have these features. Taylor and colleagues seemed to conclude that external beam radiation therapy was harmful. However, external beam radiation therapy was only considered in a subset of patients with poor prognostic features. Another interpretation of the same data is that external beam irradiation did not reverse these negative prognostic features. It seems unlikely that the treatment actually accelerated tumor growth.

Thyroid cancer is relatively uncommon and the National Thyroid Cancer Treatment Cooperative Study Register is in the unique position to promote innovative interventional studies. It is hoped that with the data base currently generated and reported, future efforts will include prospective, well-controlled, interventional clinical trials. ❖

For patients with high-risk papillary or follicular thyroid cancer, which of the following statements is true?

a. Thyroid lobectomy and external beam radiation is as effective as total thyroidectomy in producing prolonged disease-free survival and overall survival.
b. Radioiodine-131 therapy as an adjunct to surgery improves overall and cancer-specific survival in follicular thyroid carcinoma.
c. A combination of surgery, radioiodine-131 and external beam radiation, is the optimal approach for most patients.
d. Radioiodine-131 is as effective at producing cures when used alone as it is as an adjunct to initial surgery.

Special Feature

Lessons in Supportive Care, IX: Treating Hot Flashes

By Tom Smith, MD

My fridays are mostly for breast cancer patients: receiving adjuvant therapy after a half-day at work, coming in for follow-up, living with recurrent disease as best they can. A uniform complaint is hot flashes—not just a little warmth, but uncomfortable sweats that interfere with work and especially sleep. I have kept a file of mostly useless, semi-homeopathic, or unevaluated therapies over the years.

Finally, however, we have some decent treatments that do not seem to be well known. The head of a new university Women's Health Program was not aware of some new treatments when I recently queried her. So, here is the evolution of one physician's thinking and the new data.

Hot Flashes are Common

From the tamoxifen trials, we know that about 40% of women will be bothered with them. Raloxifene (which seems to be getting prescribed for adjuvant hormonal therapy without much evidence—but that's another story) causes hot flashes in about 25% of women.

In my standardized breast cancer patient review of systems, including hot flashes, sexual function, etc., hot flashes are remarkable in their prevalence.

And, it's not just women anymore. For men receiving neo-adjuvant hormonal therapy for prostate cancer, 80% had hot flashes, and 11% continued with them after the hormone treatments stopped. (Schow DA, et al. *South J Med* 1998;91:855-857.)

Hot Flashes may be Important for Compliance

Forget the discomfort for a minute, since we oncologists ask our patients to put up with an amazing variety of symptoms. Hot flashes may be one of the reasons why 6% of patients simply cannot tolerate tamoxifen. In the Italian trial of tamoxifen as a chemopreventative, temporary discontinuation was common (5.4%) and about one-fourth of those who stopped did so permanently. (Veronesi A, et al. *Tumori* 1998;84:372-375.)

OK, What Works?

Venlafaxine hydrochloride (Effexor), 12.5 mg bid works. This is 10-20% of the dose used for depression. It reduced the number of hot flashes from 6.6 to 4.3 per day. Fifty-four percent of these 28 patients had a decrease in the numbers of 50% or more. The average number of severe/very severe hot flashes declined from 1.4/d to 0.1/d. (Loprinzi CL, et al. *J Clin Oncol* 1998;16:2377-2381.) Some healthcare plans may not cover it for depression—hoping to reduce costs by stocking only a few anti-depressants—but, sometimes, an explanation of its benefits will convince them to cover it for a particular patient. Patients are often willing to pay $30 for a trial prescription.

Megestrol acetate 20 mg bid works. In a placebo-controlled trial, 74% of patients had a decrease of 50% or more compared to 20% with placebo. The only side effect was estrogen withdrawal bleeding 1-2 weeks after stopping the megestrol acetate. (It is especially important to warn vigilant or hypervigilant women who are worried about endometrial cancer from tamoxifen. The rate of 1/100 women over 5 years developing endometrial cancer is not reassuring to them.) (Loprinzi CL, et al. *N Engl J Med* 1994;331:347-352.) Recent updates from this trial confirm that 45% of patients continued to use megestrol acetate at three years, usually less than 20 mg daily. Some episodes of chills, weight gain, vaginal bleeding, and carpal tunnel syndrome were reported but the drug appears to be well tolerated in the long term. (Quella SK, et al. *Cancer* 1998;82:1784-1788.)

Vitamin E does not work, or at least does not work well enough to recommend it. (Barton DL, et al. *J Clin Oncol* 1998;16:495-500.) The one placebo-controlled trial showed that vitamin E was not preferred over placebo, and that vitamin E and placebo had a similar reduction in hot flashes (25% vs 22%, NS.) In the subsequent cross-over period, one less hot flash per day was seen in those who crossed over to vitamin E. To my review, this negative randomized clinical trial negates all the anecdotal evidence that vitamin E helps (after all, that is why we do randomized, placebo controlled trials!) but since there was no toxicity, many of my patients still take vitamin E.

Clonidine works. Oral doses of 0.1-0.4 mg bid reduced the occurrence of hot flashes 46%. (Lauffer LR, et al. *Obstet Gynecol* 1982;60:583-585.) Only the 0.2 and 0.4 mg doses had enough effect to be worthwhile, and four of 10 patients discontinued the drugs due to nausea, fatigue, irritability, and dizziness. I had patients start with one-fourth of a 1.0 mg pill bid.

Clonidine transdermal patches work. The clonidine transdermal therapeutic system reduced the frequency of hot flashes from 80% to 36% compared with placebo, with similar improvements in severity. (Nagamani M, et al. *Am J Obstet Gynecol* 1987;156:561-565.) Side effects were minimal with no significant changes in blood pressure or pulse rate.

Placebo works! About 20-30% of patients will have partial abatement of hot flashes—which is why placebocontrolled trials are so important.

Table

Summary of the Data

Drug	% Reduction in hot flash score
Venlafaxine 12.5 mg bid	55
Megestrol acetate 20 mg bid	85
Clonidine patches	33
Placebo	21-25

Modified from Loprinzi CL, et al. *J Clin Oncol* 1998;16:2377-2381.

The Take Home Message

Hot flashes are common in men and women undergoing hormonal changes. Hot flashes bother people, both men and women. There is effective therapy available, with minimal side effects. We should routinely add, "Are you having hot flashes?" to our review of systems for each person on hormonal therapy and, if the hot flashes are bothering them, prescribe some effective treatment. ❖

In Future Issues:

A Better Way to Give Gemcitabine?