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Temozolomide and Radiotherapy for Brain Metastases

ABSTRACT & COMMENTARY

Synopsis: *The treatment of choice for multiple brain metastases is whole-brain radiotherapy. Patients with medically or technically inoperable solitary brain metastases also receive radiotherapy. Efforts to enhance the effects of radiotherapy via concomitant systemic therapy have been unsuccessful. Investigators in Greece reported their phase 2 trial results showing a significant increase in the response rate of lesions in patients who received combined modality therapy using radiotherapy and temozolomide.*

Source: Antonadou D, et al. *J Clin Oncol*. 2002;20:3644-3650.

ANTONADOU AND COLLEAGUES AT THE METAXAS CANCER HOSPITAL in Piraeus, Greece, randomized 52 patients with previously untreated brain metastases to radiotherapy alone vs radiotherapy with temozolomide. Patients with life expectancies exceeding 3 months were accrued from October 1999 through June 2000. All patients had breast cancer or lung cancer, including either small cell or non-small cell carcinoma (NSCLC). Every patient had brain metastases as documented on CT or MRI scan. Demographic and functional status was well balanced between the 2 arms. Temozolomide was selected because it is an alkylating agent known to readily penetrate the blood brain barrier and may act as a radiosensitizer. Twenty-three patients received RT alone, and 25 were randomized to combined therapy. Two patients from the initial 52 randomized to either group (n = 4) refused treatment, leaving 48 patients. Median age was 61-62 years. Thirty percent of the RT patients and 20% of the combined therapy patients had known metastases elsewhere. Two thirds of patients in each group had NSCLC. Multiple brain metastases were identified in 70% (n = 16) of the RT arm and 76% (n = 19) of the combined-therapy arm.

All patients received 40 Gy whole brain radiotherapy using 12MV photons at 2 Gy per fraction. During RT, the combined therapy patients were given TMZ 75 mg/m^2/d, followed by 200 mg/m^2/d per 5-day cycle for 6 cycles as consolidation. The lowest dose of steroids necessary to maintain neurologic stability was used throughout RT, and then tapered. Anticonvulsants and anti-emetics

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were prescribed as needed.

There were 45 evaluable patients. Median follow-up was 4 months. Eighty-seven percent (n = 42) of patients died by the conclusion of the study. No patient received chemotherapy aside from TMZ following RT. Patients were assessed via monthly CT or MRI and neurologic examination. Responses were determined based on patient status at 2-months post-RT, and were confirmed 1 month later. Two radiologists blinded to the randomization centrally reviewed all scans.

Five parameters were used to compare treatment efficacy. Those were the objective response rate on imaging, including complete and partial responses; improvement in neurologic status; diminished reliance on anticonvulsants and anti-emetics; median overall survival; and cause of death. In the RT-alone arm, there were 7 complete responses (33%) and 7 partial responses (33%), along with 5 patients who had stable disease (24%). The combined therapy group exhibited a statistically significantly higher objective response rate ($P = 0.017$) with 9 CRs (38%) and 14 PRs (58%), along with 1 patient who had stable disease. Despite the higher proportion of combined therapy patients who manifested an improvement in their neurologic status (15% vs 9%), the change in symptomatology was not great enough to declare a statistical difference. In terms of reliance on steroids and anticonvulsants, RT-alone patients used 9% less steroids and 14% less anticonvulsants by the time of their final evaluation, in comparison to 33% less steroids and 40% less anticonvulsants in the combined-therapy arm. Side effects from the TMZ included headache, nausea, vomiting, and mild-to-moderate, reversible, myelosuppression in a small number of patients. Median overall survival was not significantly different between groups at 7 months for the RT-alone arm and 8.6 months for the RT/TMZ arm ($P = 0.45$). Finally, while 86% of RT alone patients died of systemic disease, so did 90% of combined therapy patients.

Antonadou et al concluded that daily temozolomide was safe and well-tolerated when combined with radiotherapy, and that its use led to a statistically significant improvement in the objective response rate. Because of their poor prognosis, it was difficult to demonstrate an improvement in survival in the patient cohort studied. The role of chemotherapy in patients with brain metastases remains controversial, and phase 3 randomized trials are needed.

COMMENT BY EDWARD J. KAPLAN, MD

Temozolomide is known to penetrate the blood brain barrier, and was recently shown to have antitumor activity as a single-agent therapy against brain metastases by Abrey, who published phase 2 results from work done at Memorial Sloan Kettering.[1] Patients received 150-200 mg/m^2/d for 5 days per 28 day cycle, just as in Antonadou et al's paper. Overall median survival for the 34 patients assessed was 6.6 months. Forty-one percent of patients achieved a partial response or stable disease. In another phase 2 trial published earlier this year by the Cytokine Working Group,[2] 31 patients with malignant melanoma metastatic to brain were treated with RT + 75 mg/m^2/d TMZ, just as in the Greek study. Additional TMZ was continued for 6 week cycles followed by 10 weeks off. Median survival was 6 months, and toxicities were limited.

The Antonadou paper was an intriguing study because its results look promising, and there were no competing therapies that could cloud the results, such as might be seen in a crossover design. The most obvious criticism is the study's small size. Even if there was a significant difference in improvement in symptomatology, it would be very difficult to detect with such a tiny sample size. Another issue that comes to mind is whether patients were evenly split

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between MRI and CT imaging. For example, if more patients in one or the other group were imaged with MRI rather than CT, a skewed CR/PR rate might result since MRI is typically more sensitive to detecting finer detail. In addition, multiple metastases can sometimes be mistaken for solitary metastases on CT, which tends to be less of a problem with MRI. Since TMZ is an oral agent that can be associated with nausea and vomiting, some patients may not have received effective amounts of TMZ despite being in the combined therapy arm. Regarding the RT, it is somewhat unusual to treat the brain with photons as high as 12 million electron volts. Usually, a brain is treated with 6 MV or similar machines. I also feel that the inclusion of patients with solitary brain lesions, who made up more than a quarter of the study population, probably diluted the results because these would seem to be the patients least likely to benefit from a synergistic effect related to TMZ. That is, in general, patients with solitary metastases have fewer symptoms and may have a longer life expectancy than patients with multiple metastases, thus making it harder to show an improvement. Finally, with almost all patients dying of systemic disease, and no patient receiving cytotoxic chemotherapy targeting extracranial disease, it will probably be impossible to demonstrate a survival advantage resulting from better CNS control until the systemic disease is better controlled.

Interestingly, an abstract of a phase 3 trial conducted by the same researchers was presented at the October 2002 ASTRO meeting in New Orleans.[3] It was well received by the attendees. The basic format was the same as in the phase 2 trial, except that the RT was delivered as 30 Gy in 10 fractions. One hundred thirty-four patients participated. Again, no survival advantage was demonstrated (8.3 vs 6.3 mo; $P = 0.18$), but the objective response rate was significantly better in the combined therapy arm (53% vs 33%; $P = 0.04$).

I am optimistic about the role of TMZ in the management of patients with brain metastases. Although it may take substantially longer to conduct, a trial looking at patients with isolated brain metastases would be the best way to assess the contribution of TMZ to their therapy. ■

References

1. Abrey LE, et al. *J Neurooncol*. 2001;53:259-265.
2. Margolin K, et al. *J Cancer Res Clin Oncol*. 2002;128: 214-218.
3. Antonadou D, et al. *Int J Radiat Oncol Biol Phys*. 2002;54:93-94.

ERT for Women with a History of Breast Cancer: Is it Safe?

ABSTRACT & COMMENTARY

Synopsis: *Investigators at MD Anderson conducted a prospective, randomized study of estrogen replacement therapy (ERT) in women with prior early stage breast cancer. Data from this study were combined with an observational series of comparable patients. ERT was associated with modest lipid and skeletal benefits but with no increase in breast cancer or compromise in disease-free survival. They conclude that larger-scale randomized studies are needed to confirm the safety of ERT for patients with a history of breast cancer.*

Source: Vassilopoulou-Sellin R, et al. *Cancer*. 2002;95: 1817-1826.

Amid the controversy of hormone replacement therapy (HRT) these days, there persists a debate on whether a woman with prior breast cancer should ever receive estrogen therapy. In the current report, Vassilopoulou-Sellin and colleagues from MD Anderson Cancer Center conducted a prospective clinical trial to assess the safety and efficacy of prolonged ERT in a group of menopausal women with localized (stage I or stage II) breast carcinoma and a minimum disease-free interval of 2 years if estrogen-receptor negative (ER-) or 10 years if ER status was unknown. For 5 years, Vassilopoulou-Sellin et al followed 77 trial participants and 222 additional women with clinical and prognostic characteristics comparable to those of the trial participants who did not wish to participate in the randomized, prospective trial. Of the eligible trial participants, 34 were randomized to receive ERT and 43 were not. In the observational group, 22 received ERT and 200 did not. Patient and disease characteristics, such as tumor size, number of lymph nodes involved, menopausal status, and disease-free interval were comparable for women who had enrolled on the trial and women who were not.

ERT consisted of Premarin (conjugated estrogen, Wyeth-Ayerst Pharmaceuticals) 0.625 mg on days 1-25 of each month. Progesterone was omitted because it might have an independent influence on the development of certain cancers or on the recurrence of breast cancer.

Thus, there were 56 women on ERT, and 2 of these (3.6%) developed a contralateral, new breast carcinoma. In the group that was not on ERT, 33 of 243 (13.5%)

developed new or recurrent breast cancer. ERT was associated with modest lipid and skeletal benefits.

Vassilopoulou-Sellin et al concluded from their findings that ERT did not compromise disease free survival in these patients who were treated previously for localized (stages I and II) breast cancer. However, they call for larger, randomized studies to confirm these findings.

COMMENT BY WILLIAM B. ERSHLER, MD

The management of breast cancer commonly involves controversial issues that take seemingly forever to resolve. An example, of course, is the decades it took to determine that modified surgical procedures produce comparable results to radical mastectomy when it comes to overall survival or local control.[1] Another controversy is whether patients with prior breast cancer could or should ever receive ERT.

The merits and limitations of estrogen replacement therapy have been discussed extensively, especially in light of the recent report from the Women's Health Initiative (WHI) study.[2] In that large, prospective randomized controlled study on the benefits and risks of combined HRT, there was a small excess in cases of breast cancer, myocardial infarction, cerebrovascular accidents, and venous thromboembolism, in conjunction with a slight diminution of the number of cases of bone fracture and colon cancer. These findings have raised the level of concern about the use of HRT in general, but methodological issues have also been raises. For example, Lamay, in a recently published editorial,[3] points out that the WHI study included a broad range of ages, and only one third were in the decade of 50-59 (the age typically in which HRT is prescribed for menopausal symptoms). He pointed out that except for venous thrombosis, the confidence intervals for outcomes were near the limit of statistical significance and that these disappear upon adjustment. Perhaps most importantly with regard to clinical practice (and the current report on breast cancer), the terminated WHI study involved the use of combined estrogen and progestin. Results of the ongoing WHI study on estrogen alone will be of great interest and importance.

The current report provides prospective data with a longer follow-up than previous reports on the use of ERT in patients with prior breast cancer. The findings reinforce the sense that ERT does not compromise disease-free survival in patients with previously treated early stage breast cancer. In the current climate, however, it will take a larger randomized study in prior breast cancer patients coupled with the safety data from the WHI study of estrogen (alone) before there is likely to be enthusiasm from the community and from practicing physicians with regard to ERT in this setting.

References

1. Fisher B, et al. *N Engl J Med*. 2002;347:1233-1241.
2. Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.
3. Lamay A. *J Obstet Gynacol Can*. 2002;24:711-715.

Anticoagulant Treatment for Cancer Patients with DVT: Risks of Recurrent Venous Thromboembolism or Bleeding are High

ABSTRACT & COMMENTARY

Synopsis: *Recurrent venous thromboembolism and/or bleeding occur in a subset of patients treated with anticoagulant therapy for deep vein thrombosis (DVT). In this report of 842 consecutive patients with DVT, 181 of whom had underlying cancer, it was shown that the presence of underlying malignancy increased the risk of recurrent DVT and hemorrhagic complications, despite standard and presumed therapeutic levels of anticoagulation. Furthermore, these risks correlated with the extent of the underlying cancer. Possibilities for improvement using the current paradigms of anticoagulation seem limited, and research investigating new treatment strategies is warranted.*

Source: Prandoni P, et al. *Blood*. 2002;100:3484-3488.

THE CURRENT STUDY FROM THE UNIVERSITY HOSPITAL of Padua, Italy, was designed to assess the risk for recurrent venous thrombosis or bleeding during anticoagulant treatment in patients with or without underlying cancer. In a prospective analysis, 842 consecutive patients with laboratory (venography or compression ultrasound) confirmed DVT were followed for 12 months to determine the rate of recurrent DVT or bleeding. Of these, 181 were known to have cancer at the time of diagnosis of DVT. The 12-month cumulative incidence of recurrent DVT in cancer patients was 20.7% (95% CI, 15.6-25.8) vs 6.8% (95% CI, 3.9-9.7) in patients without cancer. Thus, the hazard ratio for recurrent DVT in patients with cancer compared to those without was 3.2 (95% CI, 1.9-5.4). The 12-month incidence of major bleeding was 12.4% (95% CI, 6.5-18.2) in patients with cancer and 4.9% (95% CI, 2.5-7.4) in patients without cancer for a hazard ratio of 2.2 (95% CI, 1.2-4.1).

The recurrence of venous thrombosis and bleeding complications were both related to the extensiveness of the cancer. Overall, the risk for recurrences was 2-3 fold increased in patients with less extensive cancer (ie, stage I or II), whereas in patients with more advanced disease (stage III or IV) the increased risk was almost 5-fold. Similarly, the risk of hemorrhage was not increased in those with early cancer (compared with noncancer patients) but was 5-fold greater in patients with extensive underlying cancer.

COMMENT BY WILLIAM B. ERSHLER, MD

The importance of this study is that it established in a prospective analysis what clinicians have long predicted—patients with cancer have a high risk for recurrent DVT and also treatment associated bleeding.[1-3] The compared groups (those with or without underlying malignancy) were comparable in every regard, and because they were consecutive patients (ie, not selected or derived from a screening program) and because all were treated with a prescribed anticoagulation protocol, the data are very strong.

In this study, both groups (patients with or without underlying cancer) had comparable intensity of anticoagulant therapy) and in approximately 75% of both groups, the level of anticoagulation was maintained in the suggested therapeutic range (INR between 2 and 3, unless thrombocytopenic, at which time the target INR was 1.5-2). In fact, the analysis revealed that the increased risk of recurrent DVT or bleeding was not due to a change in intensity of anticoagulation therapy in the cancer group, or associated with more frequent nontherapeutic (over or under) INRs.

The correlation of recurrent DVT or major bleed with the extensiveness (stage) of the underlying malignancy supports the contention that the cancer itself contributes to anticoagulant treatment failure (recurrent DVT) or complication (bleeding). Possible mechanisms that would explain these associations include bleeding at the site of cancer, procoagulant states induced by the cancer, and decline in general condition leading to immobilization.

Thus, the Padua group has confirmed that recurrent DVT and hemorrhagic complications are more frequent in DVT patients with underlying malignancy, and that these both occur more commonly in those with advanced disease, even at a presumed therapeutic level of anticoagulation. What the research has not been able to provide is a suggestion on how to avoid these complications. Certainly, less intensive anticoagulation will result in more recurrent DVTs and more intensive anticoagulation will result in more bleeding. Placement of inferior vena cava filters may reduce the risk of pulmonary embolus, but the risk of recurrent DVTs will remain, or perhaps even be increased.[3,4] The Padua study did not include enough patients with cancer to determine if certain types are more likely to be associated with anticoagulation failure or complication. Accordingly, more research is clearly needed to identify those at highest risk, and to examine new treatment strategies to reduce these untoward complications.

References

1. Prandoni P, et al. *Ann Intern Med*. 1996;125:1-7.
2. Carson JL, et al. *N Engl J Med*. 1992;326:1240-1245.
3. Simioni P, et al. *Blood*. 2000;96:3329-3333.
4. Decousus H, et al. *N Engl J Med*. 1998;338:409-415.

Paclitaxel/Carboplatin with Paclitaxel/Cisplatin in Patients with Advanced Non-Small-Cell Lung Cancer

ABSTRACT & COMMENTARY

Synopsis: *This is the first trial comparing carboplatin and cisplatin in the treatment of advanced NSCLC. Although paclitaxel/carboplatin yielded a similar response rate, the significantly longer median survival obtained with paclitaxel/cisplatin indicates that cisplatin-based chemotherapy should be the first treatment option.*

Source: Rosell R, et al. *Ann Oncol*. 2002;13:1539-1549.

Cisplatin has been a backbone of chemotherapy combinations in non-small-cell lung cancer (NSCLC), and several combinations of cisplatin-based chemotherapy are used in the current treatment of this disease. In the United States, carboplatin has been used extensively in place of cisplatin, but there have been very few randomized trials comparing these drugs.[1] There have been a number of studies and meta-analyses that document the importance of platinum compounds.[2] The substitution of carboplatin for cisplatin has been studied in other malignancies, particularly ovarian cancer. The drugs are not equivalent in all situations. The present study is a randomized, multicenter European trial comparing paclitaxel/carboplatin vs paclitaxel/cisplatin. The major end point is objective response rate with secondary end points of survival, toxicity, quality of life, and the analysis of prognostic factors including histology.

There had been some question for many years whether chemotherapy is beneficial in patients with advanced NSCLC. There are conclusive studies that have shown a definite survival advantage in patients receiving chemotherapy compared to best supportive care. This includes cisplatin-containing regimens, vinorelbine compared to fluorouracil plus leucovorin and docetaxel as a second-line agent.[3-7] The current study was undertaken to determine the relative benefits of the 2 platinum compounds. The trial included untreated patients with NSCLC with stage IIIB or IV disease, and ECOG PS 0-2 with measurable (or nonmeasurable but assessable) disease. Six hundred sixteen patients were randomized. Patients on the paclitaxel/cisplatin arm received on day 1 paclitaxel (200 mg/m^2 for 3 h) followed by cisplatin (80 mg/m^2 for 30 min) and patients randomized to paclitaxel/carboplatin received the same dose of paclitaxel followed by carboplatin (AUC 6 for 30 min). Treatment was administered in 21-day cycles. Patient characteristics were well balanced and 17% of patients had PS of 2. The overall results are shown in the Table. Greater than 80% of patients received 90% of the schedule paclitaxel dose intensity. There were similar results with the platinum drugs. The only significant difference in toxicity was thrombocytopenia in the carboplatin-containing arm. There were no significant differences in global health status or in the functional scales, which are global indices of quality of life. The differences in survival were small but statistically significant, leading Rosell et al to conclude that the cisplatin-containing arm is superior. In the accompanying editorial, Soria and Le Chevalier indicate that carboplatin is probably a slightly inferior drug to cisplatin in NSCLC. However they also state there are many circumstances in which carboplatin would be an acceptable alternative (ie, renal insufficiency, hearing loss, preexisting neuropathy, etc).[8]

There have now been a number of trials attempting to compare cisplatin with carboplatin in NSCLC. A series of ECOG trials in the 1980s demonstrated carboplatin superiority.[9] In a recent 4-arm ECOG trial, the response rate and survival did not differ significantly between patients receiving paclitaxel/cisplatin and those in any of the other 3 arms (cisplatin and gemcitabine, cisplatin and docetaxel, or carboplatin and paclitaxel).[10] In this European randomized trial cisplatin was superior. The differences in these trials could be patient selection, histology (squamous vs adeno), dose of carboplatin, length of paclitaxel infusion (3 vs 24 h), dose of paclitaxel or supportive care. It seems that the differences between the 2 agents are minimal and may be insignificant in terms of survival. The real differences are in the toxicity profiles. The treating physician must decide on which agent to use based on their patient's tolerance and in particular comorbid illnesses. It is questionable whether further studies comparing these 2 drugs should be performed. There are currently trials evaluating nonplatinum-containing combinations.[11] It seems that a therapeutic ceiling is being reached with standard chemotherapy. Overall the trials seem to indicate an approximate 1-year survival in advanced NSCLC of about 30%. Newer treatment strategies are needed to overcome the limits of our current drug therapy. ■

Table

Trial Data

	Paclitaxel + Carboplatin	Paclitaxel + Cisplatin	*P* value
RR	25%	28%	.45
PFS	3 mo	4.2 mo	0.035
1-year survival	33	38	—
Median survival	8.2 mon	9.8 mon	0.019

References

1. Choy H, et al. *Cancer*. 2000;88(6):1336-1346.
2. Non-small Cell Lung Cancer Collaborative Group. *BMJ*. 1995;311(7010):899-909.
3. Souquet PJ, et al. *Lancet*. 1993;342(8862):19-21.
4. Marino P, et al. *Chest*. 1994;106(3):861-865.
5. Rapp E, et al. *J Clin Oncol*. 1988;6(4):633-641.
6. Shepherd FA, et al. *J Clin Oncol*. 2000;18(10):2095-2103.
7. Crawford J, et al. *J Clin Oncol*. 1996;14(10):2774-2784.
8. Soria JC, Le Chevalier T. *Ann Oncol*. 2002;13(10):1515-1517.
9. Bonomi PD, et al. *J Clin Oncol*. 1989;7(11):1602-1613.
10. Schiller JH, et al. *N Engl J Med*. 2002;346(2):92-98.
11. Herbst RS, et al. *Cancer*. 2002;95(2):340-353.

Survival after Laparoscopy in Women with Endometrial Cancer

ABSTRACT & COMMENTARY

Synopsis: *Although longer follow-up is needed, the survival of women with early stage endometrial cancer does not appear to be worsened by laparoscopy.*

Source: Eltabbakh GH. *Cancer*. 2002;95:1894-1901.

ELTABBAKH RETROSPECTIVELY REVIEWED WOMEN presenting with clinical stage I endometrial can-

cer (according to the 1988 FIGO staging) at the University of Vermont. Women treated with laparoscopic surgery were compared with those treated with laparotomy with regard to their characteristics, surgical procedure, treatment, surgical stage, histology, tumor grade, and recurrence-free and overall survival. Factors affecting survival (surgical approach, histology, grade, and surgical stage) were evaluated using multivariate analysis. One hundred women underwent laparoscopy, and 86 underwent laparotomy from January 1996 through June 2001. Both groups were similar with regard to age, parity, menopausal status, lymphadenectomy, surgical stage, tumor grade, histology, and postoperative radiation therapy. Women who underwent laparoscopy and those who underwent laparotomy had similar 2-year and 5-year estimated recurrence-free survival rates (93% vs 94% and 90% vs 92%, respectively), as well as similar 2-year and 5-year overall survival rates (98% vs 96% and 92% vs 92%, respectively). There was no apparent difference with regard to the sites of recurrence between both groups. In univariate and multivariate analyses, surgical stage, tumor grade, and histology (but not the surgical approach) were found to have a significant effect on survival. Eltabbakh concluded that, although longer follow-up is needed, the survival of women with early-stage endometrial cancer does not appear to be worsened by laparoscopy. As one would expect, surgical stage, tumor histology, and tumor grade were found to significantly affect survival regardless of the surgical approach used.

COMMENT BY DAVID M. GERSHENSON, MD

Surgery remains the cornerstone of treatment for endometrial cancer. With the innovations in optics and equipment associated with laparoscopy over the past decade or so, new surgical approaches using LAVH + BSO and surgical staging have been explored by several groups worldwide. Since the early 1990s, several of these groups, including Dr. Eltabbakh's, have reported their experience in patients with early-stage endometrial cancer. A summary of the literature to date suggests that, compared with laparotomy, laparoscopic surgery for endometrial cancer is feasible, is associated with shorter length of hospital stays and less time off work, is associated with equivalent complication rates, and is associated with an enhanced quality of life. Furthermore, these groups have demonstrated that comprehensive surgical staging with bilateral pelvic lymphadenectomy and paraaortic lymphadenectomy is also feasible and results in resection of an equivalent number of lymph nodes compared with laparotomy. Some reports have also documented that laparoscopic surgery for endometrial cancer is safe in obese patients and in elderly patients. Based on encouraging information arising from these early reports, the Gynecologic Oncology Group (GOG) initiated a large randomized trial (Lap 2) comparing laparoscopic surgery with traditional laparotomy in women with early-stage endometrial cancer. Although this study is accruing patients at a very high rate, it will likely be a few years before we have mature data regarding sites of recurrence and overall survival. Other small studies have demonstrated equivalent survival rates in patients undergoing laparoscopic surgery vs laparotomy for endometrial cancer. To my knowledge, this is the largest study reported to date. However, the median duration of follow-up among women in the laparoscopy group was only 27 months—too brief to make a determination. In addition, the study is retrospective and likely does not include a large enough number of patients to demonstrate a difference in survival. It should be noted that there have not been any port site recurrences in the present study thus far. The findings of this study are of great interest, but only with the completion of the GOG's Lap 2 will the survival issue be definitively answered. ■

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CME Questions

22. In the study from Vassilopoulou-Sellin and colleagues at MD Anderson, estrogen replacement therapy for patients with a history of early stage, treated breast cancer was shown to:

a. extend overall survival, but only for those with ER+ tumors.
b. increase new tumor development when compared to those who did not receive ERT.
c. have no effect on new tumor development or disease-free survival when compared to those who did not receive ERT.
d. be associated with an increase in cerebrovascular accidents, myocardial infarction, and thrombosis, but have no effect on breast cancer recurrence.

23. Which of the following was found to be significantly different in favor of the RT/TMZ arm in the Antonadou brain metastases trial?

a. Overall survival
b. Neurologic improvement
c. Objective response rate
d. None of the above

24. Regarding the brain metastases paper, which statement is correct?

a. Most patients in the trial died of systemic rather than CNS disease.
b. Overall survival was 6-8.6 months.
c. The results correspond to findings noted in other recent papers exploring a similar approach.
d. All of the above

25. Which of the following statements about the occurrence of recurrent thromboembolism or hemorrhagic complication in anticoagulated patients with DVT is *not* true?

a. The risk for recurrent DVT is approximately 5-fold for those patients with underlying advanced cancer when compared to those without cancer.
b. The risk for major bleed is approximately 5-fold for those patients with underlying advanced cancer when compared to those without cancer.
c. The increased risk of bleeding in anticoagulated DVT patients with underlying cancer is due to more intensive anticoagulant treatment strategies.
d. The increased risk of recurrent thromboembolism in anticoagulated DVT patients with underlying cancer is *not* due to less intensive anticoagulant treatment strategies.

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