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Treatment Implications of Chromosomal Analysis in Anaplastic Oligodendrogliomas

ABSTRACT & COMMENTARY

Synopsis: *Malignant brain tumors in adults are typically poorly responsive to chemotherapy. However, some patients with oligodendrogliomas respond well to chemotherapy, at times achieving durable complete remissions without the use of radiation therapy. This study reports the experience in 50 patients with histologically diagnosed anaplastic oligodendrogliomas, 48 of whom were treated with PCV chemotherapy. Chromosomal analysis was performed on paraffin-imbedded tissue. Isolated loss of 1p and 19q was associated with a 100% objective response rate in 17 patients. Median duration of response was greater than 31 months and median survival from diagnosis was greater than 123 months in this population. Patients with a loss of 1p who have other chromosomal abnormalities still respond to treatment, but their response durations are not durable. Patients in whom 1p was intact have much lower responses to chemotherapy with median response durations of less than 8 months. It is suggested that therapeutic decisions at the time of diagnosis can be based on the genetic subtype identified.*

Source: Ino Y, et al. *Clin Cancer Res*. 2001;7:839-845.

Malignant gliomas have been classified on the basis of their histological appearance as astrocytomas, oligodendrogliomas, ependymomas, or mixed gliomas. For each type, surgical resection and radiation have typically been the mainstays of treatment. Cytotoxic chemotherapy has played a relatively minor role because responses are typically infrequent and, when they occur, brief. However, patients with oligodendrogliomas are much more likely to have a radiographically documentable response to chemotherapy, and some patients have had dramatic and gratifying long-term durable responses. Histological evaluation of patients with oligodendrogliomas has not provided prognostic criteria to identify those patients likely to respond. Allelic loss of chromosome 1p has been reported to correlate with response to chemotherapy and longer survival.[1,2] Patients who lose 19q in addition to losing 1p may have partic-

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ularly prolonged survival.[2] In an effort to further identify biological subtypes by chromosomal analysis, Ino and colleagues, using formalin fixed paraffin embedded sections, carried out analyses for 1p, 19q, 10q, PTEN alteration, CDKN2A deletion, EGFR amplification, and TP53 mutations. Forty-eight of the 50 patients received chemotherapy with PCV. Thirty-four of these patients received radiation after chemotherapy, 5 received radiation concurrent with chemotherapy, and 11 were not irradiated. Median follow-up time from diagnosis was 107 months. Twenty-five patients responded to chemotherapy with 10 being complete responses. Of the 50 patients, 38 had tumors that were evaluable for radiographic response to chemotherapy. Response to chemotherapy was defined as radiographic decrease in tumor size of ≥ 50% or the absence of disease progression 6 months after the start of chemotherapy. Four groups were identified. Groups 1 and 2 were characterized by 1p loss, while groups 3 and 4 had 1p intact. Group 1 included those patients whose chromosomal alterations involved only a loss of 1p and 19q. Group 2 included patients with 1p loss and some other genetic alteration. Group 3 included patients with 1p intact but with a TP53 mutation, while group 4 included patients with 1p intact and no TP53 mutation. Response rate and durations of response in groups 1-4 were 100%, 100%, 33%, and 18% and 31 months or longer, 11 months, 7 months, and 5 months, respectively. Ring enhancement was a strong negative predicator for response and segregated with 10q loss, PTEN alteration, CDKN2A deletion, and EGFR amplification as predictors of poor response to chemotherapy. Patients in group 1 typically had durable responses to chemotherapy. Patients in group 2 also responded to chemotherapy, but these responses were less durable. Patients in group 3 responded less frequently, and when they did, responses were of brief duration. Finally, the patients in group 4 seldom responded to chemotherapy and had an extremely poor prognosis.

COMMENT BY MICHAEL J. HAWKINS, MD

This study extends previous work in this area, demonstrating the prognostic significance and therapeutic implications of chromosomal analyses in patients with oligodendrogliomas. Treatment was relatively uniform with all patients initially receiving chemotherapy, with 48 (96%) treated with PCV. The relatively large number of patients with histologically similar tumors that were treated in a similar fashion permitted the definition of 4 distinct groups with differing responses to chemotherapy and/or survival durations. Many patients with isolated 1p, 19q loss were doing well with chemotherapy alone. In this group, with close follow-up, radiation therapy could possibly be delayed until tumor progression is documented. Patients in group 2 also have a high response to chemotherapy, but these responses tend to be less durable and would be expected to benefit from consolidatative or concurrent radiation therapy. Patients in group 3, while having a survival that is similar to those in group 2, tend to respond less well to chemotherapy. Patients in group 4 had particularly aggressive tumors and appeared to receive little or no benefit from PVC chemotherapy. ❖

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Clinical Oncology Alert, ISSN 0886-7186, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston.
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GST Registration Number: R128870672.
Periodical postage paid at Atlanta, GA.

POSTMASTER: Send address changes to *Clinical Oncology Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $37.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

United States
$269 per year (Student/Resident rate: $105).

Multiple Copies
1-9 additional copies: $197 each; 10 or more copies: $175 each.

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Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Ershler is on the speaker's bureau for Wyeth and does research for Ortho Biotech. Dr. Roberts is a contractor for Eli Lilly and Agouron and is a consultant for Novartis Pharmaceuticals. Dr. Albertini does research for Powder Ject vaccines, Inc and Lexigen Pharmaceuticals. Drs. Hawkins, Kaplan and Roberts report no relationships related to this field of study.

FDG-PET Staging of the Axilla in Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *The majority of patients with early breast cancer are free of nodal metastases at the time of axillary dissection. Sentinel node biopsy, a minimally invasive procedure, has decreased the morbidity associated with axillary dissection in instances where the sentinel node is not involved with cancer. However, PET scanning may prove to be an entirely noninvasive alternative to facilitate identification of patients who can safely be spared any axillary surgical staging. This study from the NCI Milan concluded that PET scanning was a reliable and accurate means of diagnosing the uninvolved axilla.*

Source: Greco M, et al. *J Natl Cancer Inst*. 2001;93: 630-635.

One hundred and sixty-seven women awaiting axillary dissection after mastectomy or quadrantectomy for T1-2 breast cancer were studied with positron emission tomography (PET) imaging at the National Cancer Institute (NCI) Milan. The outcomes were then correlated with the histologic findings following Level I-III axillary dissection, and determinations were made regarding the accuracy of PET scanning for staging of the axilla. The mean patient age was 54 years (range, 28-84), and the mean primary tumor diameter was 2.1 cm (range, 0.5-5). A mean of 23 lymph nodes was recovered from the study group (range, 9-49). The breast and the axilla were in the study field. Three nuclear-medicine physicians concurred on the status of each PET scan, ie, positive or negative for disease in the axilla. PET scanning was performed after 5 hours of fasting to minimize serum insulin levels. Lymph nodes were sectioned into 2 or 3 parts and stained with hematoxylin and eosin (H&E).

Overall, 72 patients (43%) were found to have involved axillary lymph nodes at the time of surgical dissection. Twenty-three of the 98 patients with T1 disease (23%) had positive nodes, while 49 of 69 (71%) patients with T2 primary lesions had nodal metastases. Only 4 patients with histologic evidence of disease had false-negative PET results. Two of these patients had tumor emboli in their nodes, and 2 had partial nodal involvement. Among patients with positive PET scans and confirmed nodal metastases, there was a range of patterns including micrometastases, single microembolic foci, and partial nodal replacement. No patients were noted to have activity in the supraclavicular region on PET imaging, but Greco and colleagues reported that some patients had uptake in the retrosternal area suggestive of internal mammary metastases.

For PET, the sensitivity, or the number of patients with proven nodal metastases divided by the number of patients with a true-positive PET scan + the number of patients with a false-negative PET scan, was 94.4%. The specificity, or number of patients with histologically negative nodes divided by the number of patients with a true-negative PET scan + the number with a false-positive PET scan, was 86.3%. The overall positive predictive value of PET was 84%, and the overall negative predictive value was 95.3%. There was no significant difference in PET performance between patients with palpable vs. nonpalpable lymph nodes.

Greco et al concluded that PET's high-negative predictive value, as reflected by its low false-negative rate, was a landmark finding which reliably, accurately, and safely permits the identification of those patients who can avoid surgical staging of the axilla. The diagnostic accuracy of PET was similar across patients with all sizes of primary lesions.

COMMENT BY EDWARD J. KAPLAN, MD

Surgical management of the axilla is primarily a prognostic maneuver, and is not generally felt to be therapeutic by design. The approach to the axilla is in a state of transition based on the rising popularity of the sentinel node biopsy procedure. If a sentinel node is found to be free of tumor, the patient is spared a more comprehensive axillary dissection. However, if the sentinel node is involved with metastases, a Level I and II dissection is still considered to be the standard of care. The American College of Surgeons Oncology Group trial, where patients with a positive sentinel node are randomized to axillary dissection vs. no further treatment, is being conducted to determine whether axillary dissection offers a therapeutic benefit.

The study by Greco et al from NCI Milan presents intriguing data on the potential use of PET scanning in selecting outpatients who can forego an axillary dissection. However, important details about the histology of their patients' primary lesions were omit-

ted. This is of interest since it has been shown that infiltrating lobular lesions are more apt to result in false-negative scans.[1] It would also have been interesting to know whether any of the false-negative PET scans of the axilla correlated with lack of 2-fluoro-2-deoxyglucose (FDG) uptake in the primary breast lesions, infiltrating lobular or otherwise. Greco et al stated that previous breast biopsies do not affect PET performance. But, unfortunately, their study design called for PET imaging postmastectomy or quadrantectomy.

Some of the claims made by Greco et al are not substantiated by their data. For example, they stated that PET provides staging information with respect to the supraclavicular and internal mammary nodal chains, as well as all 3 axillary levels, and that it can quantify metastatic involvement. In fact, none of their patients exhibited uptake in the supraclavicular region, so any comments would be speculative. Among those patients that exhibited uptake in the retrosternal area, none had a dissection there, so no conclusions can be drawn. Furthermore, no information was provided about what levels the involved axillary lymph nodes were taken from, or whether PET imaging could distinguish nodes by level or number. Greco et al also stated that quality of life is greatly improved based on the noninvasive nature of PET scanning, but no objective support for that statement was provided. Finally, it is difficult to believe that 4 patients with mere microembolic foci in their nodes had true-positive PET scans, when others write that PET scan resolution is limited to lesions greater than 1 centimeter in diameter.[2,3]

The role of PET-scan staging in the management of the breast cancer patient will largely depend on whether axillary dissections are ultimately determined to be diagnostic or therapeutic. Since the false-negative rate for PET-scan evaluation of the axilla seems to match that of sentinel node biopsies, PET scanning could become the diagnostic method of choice. If axillary dissection is associated with a therapeutic advantage, then it is doubtful that PET staging will become widely accepted. Meanwhile, the Health Care Financing Administration is considering whether to approve Medicare reimbursement for PET-scan staging of breast cancer. ❖

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Tubal Ligation Shown to Reduce Incidence of Ovarian Cancer for BRCA1 Carriers

ABSTRACT & COMMENTARY

Synopsis: *Ovarian cancer occurs frequently in women who carry the BRCA1 and BRCA2 gene mutations. In this multinational, retrospective, case-control study, a prior tubal ligation was shown to provide significant protection against subsequent ovarian cancer development. Thus, tubal ligation is a feasible option to reduce risk of ovarian cancer in women with BRCA1 mutations who have completed childbearing.*

Source: Narod SA, et al. *Lancet*. 2001;357:1467-1470.

The lifetime risk for ovarian cancer in women who carry mutations in the BRCA1 or BRCA2 genes is high; estimated to be 40%[1] and 25%[2] respectively. About 10% of all new cases of ovarian cancer in North America are associated with mutations in these genes.[3] In several case control and prospective studies, tubal ligation has been associated with decreased risk of invasive epithelial ovarian cancer, but risk reduction had not previously been demonstrated for those genetically predisposed, such as with BRCA1 or BRCA2 mutations. Thus, the Hereditary Ovarian Cancer Clinical Study Group performed a matched case control study among women who had undergone genetic testing and who carried a pathogenic mutation in BRCA1 or BRCA2. Cases were 232 women with a history of invasive ovarian cancer and controls were 232 women without ovarian cancer. Cases and controls were matched for year of birth, country of residence, and mutation (BRCA1 or BRCA2).

The median age at which ovarian cancer was diagnosed was 51 years (range, 24-81) and the study was performed at a median of 5 years after diagnosis. Tubal ligation was reported by 39 of the ovarian cancer patients compared to 69 of the controls. Of the participants with BRCA1 mutations, significantly fewer patients than controls had ever had tubal ligation. This association remained significant after adjustment for oral contraceptive (OC) use, parity, personal history of breast cancer, and ethnic group. Among BRCA2 carriers, tubal ligation was not found to reduce risk significantly.

Also demonstrable in this study was a strong protective effect of OCs, and this was evident for carriers of

either BRCA1 or BRCA2 mutations. The combination of OC use and tubal ligation offered the greater protection than either method alone. Among BRCA1 mutation carriers, tubal ligation and a history of OC use, compared with neither exposure, was associated with an odds ratio of 0.28 (0.15-0.52; $P < .0001$).

COMMENT BY WILLIAM B. ERSHLER, MD

Tubal ligation has been associated with a decreased risk of ovarian cancer. For example, after 12 years of follow-up in the Nurses Health Study,[4] a strong inverse relation between tubal ligation and ovarian cancer was seen. There have been several case control studies that were reviewed in a meta-analysis,[5] and again, there appeared to be decreased risk of ovarian cancer in those that had received tubal ligation. The current study adds the important information that the protective effect is evident in those with high risk, those with BRCA1 mutations. The study did not show a significant effect for those carrying BRCA2 mutations, most likely because of the smaller number of participants with this mutation (59 of the 232 cases), and the later onset of ovarian cancer in those with this mutation. The age at tubal ligation was important, with the greatest effect observed in those who had this procedure at a younger age. However, a significant protection was observed even in those who had the procedure at a later age.

This report also confirmed the strong protective effect of prior use of OCs. In fact, the risk reduction for those who had used OCs and had a tubal ligation was 72% when compared to those who had neither interventions.

The mechanism whereby tubal ligation protects against ovarian cancer development is a matter of conjecture at present. A variety of hypotheses have been proposed that implicate an altered hormonal microenvironment or reduced inflammation, but a definitive explanation awaits experimental demonstration.

Methods of preventing ovarian cancer in women with or without these genetic predispositions include prophylactic oophorectomy, chemoprevention with OCs, or regular screening (eg, by ultrasound and serum CA-125). OCs alone have been shown to reduce risk by approximately 50%,[6] but some physicians and patients are concerned about the potential increased risk of breast cancer by such an approach.

Currently, and as clearly supported by this report, tubal ligation offers protection for women at high risk of developing ovarian cancer (particularly those with BRCA1 mutations). In such women who have completed childbearing, tubal ligation with or without continued OCs would seem a logical recommendation. ❖

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Matched, Unrelated Bone Marrow Transplants Prove Equivalent for Patients with Chronic Phase CML

ABSTRACT & COMMENTARY

Synopsis: *Transplantation of bone marrow from unrelated but matched donors has been previously reported to be associated with less favorable clinical outcomes when compared to those from matched sibling donors. In this report from the transplant program at the University of Minnesota, the data from 141 consecutively treated chronic myelogenous leukemia patients were examined to determine if there was a difference in outcome for those receiving unrelated marrow. This was a retrospective, uncontrolled review, but the data suggest comparable clinical outcomes for recipients of matched, unrelated bone marrow.*

Source: Davies SM, et al. *Am J Med*. 2001;110: 404-405.

The purpose of the report from the transplantation program at the University of Minnesota was to examine their accumulated experience with allogeneic bone marrow transplantation for chronic myelogenous leukemia (CML) with regard to the clinical outcomes using matched but unrelated donors compared with matched, related donors. The experience between 1983 through 1997 of 141 (96 matched, sibling donor and 45 matched, unrelated donor) transplants for chronic phase CML was reviewed. All were HLA-A,B/DRB1 matched. The median age of matched sibling donor recipients was 38 years (range, 8-56) and of unrelated donor recipients was 35 years (range, 3-53), and the median range of follow-up was 6 years (range, 1-15) in matched sibling donor recipients and 5 years (range, 2-10) in unrelated donor recipients.

There was no significant difference in the 5-year sur-

vival rates of matched sibling donor recipients (58%; 95% confidence interval [CI], 48-68%) and unrelated donor (53%; 95% CI, 39-67%; *P* = .4). Among people who underwent transplant within 1 year after diagnosis, the 5-year survival rate of matched sibling donor recipients (76%; 95% CI, 65-87%) was not significantly different (*P* = .5) from that of unrelated donor recipients (70%; 95% CI, 52-88%). In multiple regression analysis, longer time from diagnosis to transplantation, T-cell depletion, and grades III or IV graft vs. host disease were independently associated with poorer survival. Transplantation of unrelated donor bone marrow was not associated with increased mortality (relative risk, 1.1; 95% CI, 0.6-2.1; *P* = .7).

COMMENT BY WILLIAM B. ERSHLER, MD

This is a retrospective review of 2 groups of early-phase transplanted CML patients; one with matched sibling donors, and the other with matched, unrelated donors. Although there are inherent difficulties in an analysis such as this, it was heartening to note the apparent success of recipients of unrelated donor transplants, comparable to those with sibling donors. The data are in contrast to earlier reports in which complications were greater and survival less for recipients of unrelated marrow,[1] but is similar to a more recent series of CML patients treated with unrelated bone marrow grafts[2] in which the survival rate at 5 years was 57% for those transplanted during early chronic phase. Presumably, the improved clinical outcomes with unrelated donors resulted from more precise methods of matching and more successful prevention and/or management of graft vs. host disease, graft failure, and late infections.

Thus, it is apparent that transplantation of bone marrow from a matched sibling donor or an HLA-A,B/DRB1-matched unrelated donor produces comparable outcomes in patients with CML, particularly if the transplant takes place within the first year. With the expansion of the national and international bone marrow transplant registries, there are now more than 6 million registered donors, and the likelihood of identifying at least one 6-antigen-matched donor is approximately 75%. Consequently, marrow transplantation during early phase CML is a reasonable, and increasingly available, treatment option.

Alternatives, of course include chemotherapies, such as hydroxyurea or busulfan, which may successfully control symptoms, but offer no curative potential and may not even prolong survival.[3,4] Interferon-alpha, administered early and in sufficient doses, has resulted in complete cytogenetic remissions, and for these patients survival is likely to be enhanced. Interferon treatment, however, may reduce the success of subsequent transplantation.[5] Patients and oncologists are anxious to hear more about the tyrosine kinase inhibitor STI 571, an oral agent that inhibits the Bcr-Abl transcript and has led to complete cytogenetic responses in many patients, particularly those in chronic phase.[6] Just where this agent will fit in the management of CML, particularly in the context of the potentially curative transplantation schemes, is yet to be established, but no doubt will be the subject of future intensive research.

In the meantime, it is reassuring to know that transplantation with unrelated marrow is producing good results. Hopefully, such will also be the case for unrelated donor transplants for other diseases, such as lymphoma and acute leukemia. ❖

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Chemoprevention of Second Primary Lung Cancers

ABSTRACT & COMMENTARY

Synopsis: *Animal models have shown that vitamin A can reverse squamous metaplasia in the setting of vitamin A deficiency. Furthermore, published data from a randomized trial from Milan showed that patients who took vitamin A following treatment for stage I non-small cell lung cancer realized a statistically significant decrease in second primary tumors of the upper aerodigestive tract. An NCI-sponsored, randomized, intergroup placebo-controlled trial based on these types of data sought to confirm whether, indeed, second primary tumors and recurrences could be prevented with adjuvant isotretinoin. It was concluded that no protective effect could be identified, and that isotretinoin might be harmful if taken by current smokers.*

Source: Lippman SM, et al. *J Natl Cancer Inst*. 2001; 93:605-618.

During the years 1992 through 1997, 1265 patients were randomized from 6 weeks to 3 years post-stage I non-small cell lung cancer resection to placebo vs. 30 mg isotretinoin (13-cis-retinoic acid)

daily for 3 years to determine whether second primary cancers and lung cancer recurrences could be prevented. Patients were stratified based on tumor histology, T-stage, and smoking status. Participating groups in this NCI-sponsored Intergroup 91-0001 trial included the RTOG, ECOG, SWOG, CALGB, NCCTG, and M.D. Anderson along with its affiliates. Based on an expected annual incidence of 2-3% for second primary tumors (SPTs), the study possessed at least an 80% power to detect a 50% reduction in SPTs. SPTs were defined as those tumors with different histology, lobe of origin, or incidence beyond 5 years as compared to the index lung tumor. After excluding patients who were implicated in a computer randomization error and those who were ineligible for participation, 1166 patients formed the basis of the study.

The median age of the study participants was 61 years (31-86). There were 57% males, 92% whites, 39% current smokers, 53% former smokers, and 68% non-squamous histologies among the participants. Median follow-up was 3.5 years. The trial was closed in February 2000 after 7 years. Multivariate analysis indicated that there were no statistically significant differences between the 2 study arms with regard to the study endpoints of SPTs and recurrences, or mortality. Both non-smoking related SPTs (GI, prostate, breast) and smoking-related SPTs (lung, head & neck, esophagus, bladder) occurred with equal frequency in both groups. Sixty-two percent of the SPTs were considered to be smoking-related, including 47 in the isotretinoin group and 44 in the placebo group. Subset analysis revealed that current smokers in the vitamin A arm exhibited a trend toward higher recurrence rates (P = .15) and a statistically significant higher mortality rate (P = .01) than their counterparts in the placebo arm. Affected participants were advised to stop taking isotretinoin despite any remaining time in their 3-year study schedule.

Lippman and colleagues concluded that the trial results were disappointing, and were a reflection of the current lack of understanding of the interaction between retinoids and bronchial epithelial cells. Longer follow-up studies are planned.

COMMENT BY EDWARD J. KAPLAN, MD

Randomized trial results published by Pastorino and associates from Italy in 1993 indicated that adjuvant retinol palmitate, at 300,000 IU daily for up to 2 years, was effective in reducing the number of smoking-related upper aerodigestive tract SPTs and might improve disease-free survival in patients who underwent resection of stage I non-small-cell lung cancers.[1] Three hundred and seven patients were followed for a median of 46 months. Thirteen smoking-related SPTs occurred in the vitamin A arm vs. 25 in the control arm. The estimated 5-year disease-free survival was 64% vs. 51% in favor of the treatment arm (P = .054).

Early results of the Italian study formed the basis of another randomized trial, the European Study on Chemoprevention with Vitamin A and N-acetylcysteine (EUROSCAN) study, which was begun in 1988.[2] Once again, 300,000 IU of vitamin A daily over 2 years was tested as a chemopreventive agent in patients treated for head and neck or lung cancer. At a median follow-up of 49 months, van Zandwijk and associates did not find any benefit associated with either vitamin A or N-acetylcysteine. They concluded that study subjects should be followed for a minimum of 10 years since the latent period for carcinogenesis is at least that long.

The Lippman study, despite its reportedly negative outcome, raises some interesting issues. They state at the end of the paper that they are not certain why the isotretinoin failed to exert the anticipated effect. Unfortunately, little or no attention was paid to the potential drawbacks of the study, or to how a follow-up study might be improved. An easy mark for criticism is the mishandled randomization, which Lippman et al themselves pointed out. Other possible confounding factors are the 15% (n = 174) of patients who were lost to follow-up, and the 40% of participants in the vitamin A arm who were noncompliant with the study design. These numbers seem to be rather high, particularly since the analysis was carried out on an intent-to-treat basis.

The intergroup trial study design called for a chest x-ray up-front to rule-out existing SPTs in the lungs. However, based on the recently published Early Lung Cancer Action Project (ELCAP) work by Henschke and colleagues from Cornell,[3] we saw that malignancies are detected 4 times as frequently on low-dose CT as on CXR. Eighty-three percent of the stage I malignancies were not detected on CXR. One can thus appreciate that there is no way to know whether the vitamin A cohort in the intergroup trial was destined to fail based on a higher number of unrecognized lung cancers at the time of randomization. Low-dose CT screening would be advisable in any new effort.

It is fairly certain, as mentioned in the EUROSCAN paper, that longer follow-up is needed before pronouncements of failure can be offered. This is highlighted by data in Pastorino et al's paper which described the average time to developing a second malignancy as 16-42 months for smoking-related SPTs and, specifically, about 2 years for lung cancers. Lippman et al's study suffers from a short (3.5 year) follow-up in relation to the timing of expected second events, which can take many years.

Just as the mechanism of action of retinoids is unclear, it is also unclear who will derive the most benefit from adjuvant vitamin A. Perhaps ongoing smoking neutralizes a beneficial effect, and perhaps never-smokers who develop lung cancer possess an intrinsic defect in their mucosa that is not amenable to correction by retinoid ingestion. A study focusing on initiation of vitamin A within 6 months of early stage lung cancer treatment in former smokers might be interesting. Lippman et al's study enrolled participants up to 3 years removed from surgery, which may have been too late to reverse incipient tumor development.

In summary, no one knows the optimal time for initiation, dosage, duration, or formulation of vitamin A that will bestow the maximum benefit on patients at risk for SPTs or recurrences. It appears that continued follow-up, as suggested by Lippman et al, and improved study design eventually will help sort out whether vitamin A is ultimately proven to offer a preventive effect against second tumors and recurrences. ❖

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CME Questions

25. Extremely high response rates to PCV occur in patients with oligodendrogliomas that exhibit which pattern of chromosomal abnormality?

a. Isolated 1p, 19q loss
b. 1p intact, 19q loss with TP53 mutations
c. Isolated TP53 mutations
d. Isolated 19q loss

26. Based on the NCI Milan data, PET scan staging of breast cancer:

a. is especially accurate in identifying patients with internal mammary nodal metastases.
b. has too high a negative predictive value to affect patient management.
c. has too high a positive predictive value to affect patient management.
d. appears to have a false-negative rate similar to that reported elsewhere for sentinel node biopsies.

27. Which of the following statements is *not* supported by data presented by Greco et al?

a. PET scans are useful in predicting the number of involved axillary lymph nodes.
b. PET scans are able to distinguish involved lymph nodes by level I-III.
c. PET scans must be performed within 2 hours of a meal to be reliable.
d. All of the above

28. Which of the following interventions has *not* been demonstrated to reduce ovarian cancer development in women with BRCA1 mutations?

a. Oophorectomy
b. Tubal ligation
c. Oral contraceptives
d. Regular screening by ultrasound and serum CA-125

29. Transplantation of unrelated (but completely matched at HLA A,B/DRB1) bone marrow for chronic myelogenous leukemia in chronic phase has been shown to:

a. produce comparable clinical outcomes as similarly matched sibling marrow.
b. produce less favorable clinical outcomes than similarly matched sibling marrow.
c. produce more favorable clinical outcomes than similarly matched sibling marrow.
d. produce more favorable clinical outcomes than treatment with the novel tyrosine kinase inhibitor (STI 571).

30. Based on data from the NCI Intergroup trial, concerns were raised that isotretinoin might exert:

a. a carcinogenic effect in nonsmokers.
b. disappointingly little, if any, effect on prevention of second primary tumors.
c. a potentiating effect on lung cancer recurrences in nonsmokers.
d. harmful cardiac effects within the first year of use.

31. Lippman et al concluded that isotretinoin use:

a. is safe in patients without prior cardiac histories but must be used with caution in those with a history of prior cardiac events.
b. is safe in patients taking 1,000,000 IU daily for prophylaxis against second primary cancers.
c. confers a preventive effect against second primary head and neck cancers, but not lung cancers.
d. cannot be recommended until further studies are done.

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *Clinical Oncology Alert*. Send your questions to: Robert Kimball, *Clinical Oncology Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Clinical Oncology Alert* via the internet by sending e-mail to robert.kimball@ahcpub.com. ❖

In Future Issues:

Mononuclear Cells Plus IL-12 as a Melanoma Vaccine