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Meta-Analysis Reveals Chemotherapy Benefit for Adults with Glioma

ABSTRACT & COMMENTARY

Synopsis: *A meta-analysis of published (and 1 unpublished) clinical trials of adjuvant chemotherapy after surgery and radiation revealed a significant, albeit modest enhancement of survival in patients with high-grade glioma. Whether examined as a total population of more than 3000 adult high-grade glioma patients or by subsections defined by age, gender, histology, or volume of residual disease after surgery, chemotherapy produced the same modest response, which by meta-analysis reached a significant level. Thus, the idea that high-grade gliomas will respond to chemotherapy and improve survival by a few months may be expected. However, additional studies are called for to determine if such enhancement in survival is of sufficient quality to warrant the risks and costs associated with treatment.*

Source: Glioma Meta-Analysis Trialists Group. *Lancet*. 2002;359:1011-1018.

A NUMBER OF INDIVIDUAL CLINICAL INVESTIGATIONS SPANNING the past 3 decades have indicated modest, if any benefit, of adjuvant chemotherapy after surgery and radiation for adults with high-grade gliomas. Thus, the UK Medical Research Council Clinical Trials Unit charged an international group of investigators (the Glioma Meta-Analysis Trialists Group) to carefully review all published and unpublished clinical trials to determine, en masse, if there is discernible benefit demonstrated by meta-analysis. Data from 3004 patients participating in 12 clinical trials that were considered suitable for this analysis were reviewed and updated. Several additional reports were examined, but these were excluded for any of a number of reasons, most notably that they did not compare directly the effects of the addition of chemotherapy upon surgery plus radiation. In the various studies, the doses of radiation and the fields treated were variable, as were the chemotherapy regimens used. In all studies, at least 1 of the drugs used was a nitrosourea. Typically the dose of radiation selected ranged from 40 to 60 Gy.

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Overall, the results indicated significant prolongation of survival associated with chemotherapy, with a hazard ratio of 0.85 (95% CI, 0.78-0.91) or a 15% relative decrease in the risk of death. This effect is equivalent to an absolute increase in 1-year survival of 6% (from 40-46%) and a 2-month increase in median survival. Surprisingly, there was no evidence that the effect of chemotherapy differed in any group of patients defined by age (< 40, 40-59, > 60), sex, histology, performance status, or extent of resection.

COMMENT BY WILLIAM B. ERSHLER, MD

Despite the infiltrative nature of high-grade gliomas that make them nearly impossible to resect and the virtual certainty that disease will recur, even after radiation therapy, the benefits of adjuvant chemotherapy in patients has been difficult to establish. Many clinical trials have been published demonstrating marginal, but not significant, enhancement in event free survival. Thus, typically, standard of care remains cytoreductive surgery followed by radiation. Yet, survival remains low, less than 1 year in most series.

The current report provides some evidence that chemotherapy may add some time beyond surgery and radiation. Although the improvement in survival was quite modest, the finding reached a level of unquestionable statistical significance. Thus, the report is yet another example of the power of carefully performed meta-analysis. In not one of the published clinical trials was there a significant enhancement of survival demonstrable, but when subjected to this type of analysis, such was unequivocally the case.

Of course, one might argue that the addition of 2 months of life for patients with high-grade gliomas by chemotherapy needs to be balanced by any impairment in quality-of-life for the several months in which the patient is treated. Yet, with the clear demonstration that chemotherapy provides survival benefit, these quality of life issues should be carefully examined and treatment regimens developed that are both tolerable and effective. Furthermore, it is now clear that gliomas are not absolutely resistant to cytoreductive chemotherapy, and new agents, particularly those that are, or can be made to be lipid soluble (and thus able to permeate the brain substance), need to be developed and tested in this population. ■

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

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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

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

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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. Albertini does research for Powder Ject vaccines, Inc and Lexigen Pharmaceuticals. Drs. Hawkins, Kaplan, Kotz, and Morris report no relationships related to this field of study. Drs. Canellos, Chabner, Einhorn, Goodman, Lippman, Pinedo, and Sutton did not return financial disclosures.

Combined Radiotherapy and Interferon Alpha 2b Can Lead to Increases in Toxicity

ABSTRACT & COMMENTARY

Synopsis: *The use of concomitant/sequential radiotherapy (RT) and interferon (IFN) as adjuvant therapy following resection of high-risk malignant melanoma appears to be increasing. This report from 3 centers in Utah pooled data in order to highlight the potential for unexpected toxicities when using this combination therapy. They recommend that clinicians remain vigilant until the radiosensitizing effects of IFN are better characterized.*

Source: Hazard LJ, et al. *Int J Radiat Oncol Biol Phys*. 2002;52:796-800.

OVER THE PAST 10 YEARS OR MORE, VARIOUS STUDIES have shown that IFN has radiosensitizing properties in vivo that can cause toxicity.[1,2] The precise mechanism for this effect is unknown. Investigators believe that accumulation of cells in the G2-M phase of the cell cycle, a radiosensitive phase, may play a role. Compromised damage repair and altered oncogene

expression might be important, too. Hazard and colleagues identified a set of unusual complications in a pooled series of 10 malignant melanoma patients treated at LDS, the University of Utah, and the Browning Cancer Center in Ogden, Utah, between 1995 and 2001. These patients received radiotherapy and IFN-alpha 2b either together or within 1 month of the completion of radiotherapy. All patients were felt to be at high risk for recurrence by virtue of either deep invasion and/or regional nodal involvement.

Six patients received IFN during RT, and the remainder received it less than a month after RT was completed. Seven patients received 2 Gy per fraction to a dose of 50 Gy, one received 1.8 Gy per fraction to 45 Gy, one received 2.5 Gy per fraction to 52.5 Gy, and one received 4 and 6 Gy fractions to a total dose of 36 Gy. All patients who received concomitant RT/IFN were given maintenance subcutaneous doses of IFN that were not otherwise specified. The others received high-dose IFN after RT, and those doses were not specified, either.

Three of the 6 patients treated concomitantly developed unexpected toxicities, including 2 with soft tissue radionecrosis and 1 with a brachial plexopathy. In the second group, among patients who received IFN following RT, one patient developed brain necrosis and another suffered from a brachial plexopathy.

Hazard et al concluded that, although their report is essentially an anecdotal review without any statistical power, there remain many unanswered questions in terms of the interactions between RT and IFN. To some extent, the effects of this combination are somewhat unpredictable, and great care should be taken when treating this kind of patient.

COMMENT BY EDWARD J. KAPLAN, MD

The IFNs are considered to be biologic response modifiers whose exact mechanism of action is unknown. They modulate cell proliferation and host immune response. Trials with IFNs began in the late 1970s, but it was not until 1995 that IFN-alpha 2b was approved by the FDA after ECOG 1684 demonstrated a survival benefit in the adjuvant setting. Advocates of IFN suffered a setback when ECOG 1690 showed a relapse-free survival benefit, but no overall survival benefit. The controversy abated after the results from ECOG 1694 published last year again showed a statistically significant RFS and OS benefit.[3] Commercially available forms of IFN are IFN-alpha 2a (Roferon-Aâ, Roche), IFN-alpha 2b (Intron-Aâ, Schering), and IFN-alpha 2c (Boehringer Ingelheim).

Like IFN, favorable results have been reported with postoperative radiotherapy used as adjuvant treatment for high-risk melanoma patients.[4] Although an occasional case report has appeared describing unexpected synergies with concomitant IFN and RT,[5] and a recent paper described an instance of radiation recall dermatitis following IFN administration 5 days after completion of 30 Gy RT to the neck,[6] few clinical trial reports on concomitant/sequential RT/IFN have been published.

A basic literature search turned up 1 completed Phase I trial on RT/IFN with cisplatin for mesothelioma (Fox Chase CC-96087) and 3 closed Phase I/II trials including: one for RT/IFN for Stage III or recurrent melanoma (Moffitt CC-11543); one for RT/IFN for high grade glioma (Cancer Biotherapy Study Group 95-08); and another for RT/IFN for Stage III NSCLC (Univ. of Rochester). Only the last study has been reported.[7] One small Phase II study from Mexico reported on RT/IFN for Stages III/IV cervix cancer,[8] and publication of the only 2 Phase III trials of which I am aware is pending. The first is RTOG-9304, which looked at RT/IFN for locally advanced NSCLC. Hazard et al provided some details of the results, including increases in Grade 3,4 acute toxicity and in Grade 4 late radiation pneumonitis in the combined modality arm. However, without the entire report, we are still not sure whether those differences were statistically significant. The other Phase III trial is ECOG 3697, which evaluated high-dose IFN with hypofractionated RT in patients with nodal metastases. This trial is closed, but the results have not been published yet.

It is difficult to know how to proceed when faced with a patient who may be a candidate for combined/sequential RT/IFN. The unexpected toxicities observed in the Hazard et al report occurred at dose levels which were not unusual, and the toxicities were fairly severe. It seems that it did not matter whether the IFN was administered with or after RT, since the percentages of patients affected were roughly the same in both groups, ie, about half. That number seems higher than what has been reported in the few papers published, but it does underscore the need for all of us to remain vigilant, and proceed with caution. Hazard et al mentioned 1 patient whom they felt developed brain radionecrosis that was attributed to IFN radiosensitization, but my understanding is that IFN exhibits poor penetration of the blood-brain barrier when no tumor is there to disrupt it.

Hazard et al have reported on an interesting phenomenon that deserves further study. Perhaps an IFN Working Group might be required to make sense of the different studies soon to be reported. It is curious that

while all phases of studies are being conducted, Hazard et al rightly point out that the optimal dose and schedule for combined RT/IFN has yet to be determined. ■

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Multifocal Breast Cancer: Sum of the Parts Equals the Whole

ABSTRACT & COMMENTARY

Synopsis: *Multifocal/multicentric breast cancer may be associated with a worse outcome than similarly staged unifocal cancers. This may be due to current staging rules that determine the T stage based on the size of the largest nodule only. This study presents data that the biology of these tumors is more closely related to the sum of the diameters of each nodule.*

Source: Andea AA, et al. *Cancer*. 2002;94:1383-1390.

ACCORDING TO THE CURRENT STAGING SYSTEM, THE T stage in multifocal/multicentric breast cancer is determined by using the size of the largest individual mass. Andea and colleagues hypothesized that the prognosis and behavior of a multifocal/multicentric breast cancer would be best determined by estimating the total tumor volume rather than using the largest lesion only. Therefore, Andea et al retrospectively identified 101 patients with multifocal/multicentric invasive breast cancer. Those with diffuse microinvasion or those in which the nodules could not be measured were excluded. Their study is entitled "Pathologic Analysis of Tumor Size and Lymph Node Status in Multifocal/Multicentric Breast Carcinoma."

Tumor "size" is conventionally estimated by the largest diameter of a mass even though tumor burden is more likely related to volume or surface area. In the study by Andea et al, the "size" of the tumor was recorded using either the standard procedure (diameter of the largest tumor nodule only) or the alternative approach (sum of the diameters of all tumor nodules present). For comparison, control cases of unifocal breast cancer were also retrospectively identified from their records.

Most of the multifocal/multicentric cancers had just 2 nodules (76%) with the remainder having 3 or 4 nodules. In cases where such information was available, 62% had tumor nodules located in the same quadrant whereas in the other 38% the nodules were in different quadrants. The histologic subtype of separate tumor nodules was different in 16% of cases. The grade of separate tumor nodules was dissimilar in 5% of cases.

The most important observation was the relationship between the risk of lymph node metastasis and "tumor size" in multifocal/multicentric breast cancer. Using standard staging rules, multifocal/multicentric carcinomas falling within the T1/T2 subgroups had a much higher risk of positive nodes compared with T1/T2 unifocal carcinomas. However, if the T stage of the multifocal/multicentric cases was calculated based on the combined diameters rather than the largest diameter alone, the incidence of positive nodes was comparable to unifocal carcinomas of similar total size. For example, unifocal T1 tumors had positive nodes in 35% of cases. Similarly, multifocal/multicentric tumors whose combined measurements were also classified as T1 had positive nodes in 33% of cases. However, multifocal/multicentric tumors classified as T1 using the standard staging classification had involved nodes in 60% of cases (P = 0.002). A multivariate analysis suggested that multifocality itself was not an independent risk factor after controlling for total tumor volume.

■ COMMENT BY KENNETH W. KOTZ, MD

In the fifth edition of the *AJCC Cancer Staging Handbook*, "multiple simultaneous ipsilateral primary carcinomas" are assigned the T stage based on the "largest primary carcinoma," and one should "enter into the record that this is a case of multiple simultaneous ipsilateral primary carcinoma" and "such cases should be analyzed separately."[1] The sixth edition is scheduled for publication by Springer-Verlag with an expected release date in May 2002.[2] The finding of separate invasive nodules in one breast has several potential explanations including: 1) intramammary metastases; 2) 2 or more independent tumors; or 3) multiple areas of invasion arising from

extensive ductal carcinoma in situ. A distinction between these entities has sometimes been implied by the terms multifocal and multicentric. For some authors, multifocal and multicentric are used to differentiate intramammary metastases from synchronous primaries, respectively.[3,4] For others, multifocal refers to tumors localized to 1 quadrant whereas multicentric means nodules in different quadrants.[4,5] And for many, the terms are used interchangeably.[3] The origin of multifocal/multicentric breast cancer has been studied using morphologic, immunohistochemical, and molecular techniques. These studies have generally shown that most multifocal/multicentric breast cancers are in fact due to intramammary metastases rather than separate primaries.[3-5] In the study by Andea et al, cases with more than 1 histology or involving more than 1 quadrant were included but not analyzed separately.

In general, treatment of multifocal/multicentric tumors parallels that of unifocal tumors. There has been concern regarding the accuracy of sentinel lymph node mapping in multifocal/multicentric tumors.[6] However, a study of 19 such patients whose sentinel node biopsies were followed by a complete axillary node dissection found complete concordance in all patients.[7] Many studies (referenced by Andea et al[4]), but not all,[5] have reported an adverse outcome in multifocal/multicentric tumors as staged by current rules. The data by Andea et al suggest that this is related to "understaging." Although limited by a retrospective design, they have found that the metastatic potential of multifocal/multicentric breast cancer is more closely related to the aggregate diameters rather than using the diameter of the largest nodule only. Even without clinical outcome data, this information might be useful in estimating systemic risk and designing adjuvant therapy. ■

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Adjuvant Chemotherapy for Older Colon Cancer Patients: From Where is the Evidence?

ABSTRACT & COMMENTARY

Synopsis: *Colon cancer is a disease of older people with the median age being close to 70 years. Adjuvant chemotherapy is beneficial in young patients as determined by clinical trial, but these trials have included disproportionately few patients older than 65 years. In the current analysis, a database that linked NCI SEER data with Medicare claims clearly demonstrated that for the approximate 50% of those older than age 65 years with node-positive colon cancer who were treated, a survival benefit comparable to younger patients was observed. The data support the use of adjuvant 5-FU in older, node-positive colon cancer patients.*

Source: Sundararajan V, et al. *Ann Intern Med*. 2002;136:349-357.

Systemic chemotherapy used in the adjuvant setting has been the standard of care for node-positive colon cancer for over a decade, since the publication of the Moertel reports[1,2] and the NIH consensus conference.[3] The final report of that phase III trial (which included levamisole with 5-FU), showed that treatment reduced the recurrence rate by 40%, the mortality rate by 33%, and did not cause detectable late side effects. Yet, in that trial, like in most large cancer treatment studies, there were a disproportionate number of young patients. It should be recalled that nearly 75% of cases of colorectal cancer are diagnosed in patients older than 65 years,[4] and yet, close to 50% of such patients (node positive, older than 65 years) are treated with adjuvant therapy.[5]

In the current report, Sundararajan and colleagues explored a derived database from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) linked with Medicare claims forms. The SEER files provided information on tumor histology and location, disease stage, individual demographic features, primary surgical and radiation treatment and survival, and the Medicare claim files provided information on diagnostic and treatment costs.

Of the 4768 Medicare covered patients older than age 65 who received a diagnosis of node-positive colon cancer from 1992-1996 in the geographically diverse sites selected by SEER for surveillance, 52% received

5-FU. For this group, the hazard ratio for death was 0.66 (95% confidence interval, 0.61-0.73). By examining Medicare claims, issues such as comorbidity or organ impairment were examined for both treated and untreated patients. Upon rigorous analysis, it was concluded that for a confounding factor to influence this result (that treated patients had improved survival), that factor would have had to have been extremely disproportionately represented in either the treatment or non treatment group. Thus, Sundararajan et al conclude that adjuvant chemotherapy for node positive elderly patients reduces death from colon cancer comparable to younger patients.

COMMENT BY WILLIAM B. ERSHLER, MD

The incidence of colon cancer is 6 times greater in individuals aged 65-84 than for adults younger than 65 years. Clinical trials that have demonstrated the efficacy of adjuvant chemotherapy are disproportionately biased toward younger patients, and in practice, it appears that a large segment of those eligible for treatment do not receive it, presumably because of existing comorbidity or impaired organ function. Certainly, justification for intervention in the older age group is not supported by the large clinical trials, from which they were not adequately represented.

Short of a clinical trial aimed specifically at elderly patients, the analysis provided in the current report may have to suffice. The SEER-Medicare database is a useful way to examine the effectiveness of treatment among elderly patients. Medicare covers almost all patients older than 65 years, and the claims provide useful and reliable data on treatments received for cancer, as well as comorbidities and other treatments. However, there are some deficiencies, including an acknowledged inaccuracy with regard to in-hospital-administered chemotherapy and the use of oral prescription drugs. (The study was concluded well before Capecitabine was introduced for the treatment of colon cancer). More importantly, the Medicare data do not include functional (eg, performance) status, criteria which oncologists and geriatricians agree are predictive of favorable clinical outcomes.

With these caveats in mind, the data presented are the best we have to support the use of adjuvant chemotherapy in elderly colon cancer patients. Oncologists should review the conclusions of this study carefully. Although derived from community practice and not a prospective, randomized trial, the database was large and the analysis careful enough to conclude that comparable clinical benefits should be expected in older patients. What remains to be established is the fine-tuning. In general, 5-FU-based regimens are both safe and effective. Nonetheless, there are some for whom the toxicities encountered might impair survival or significantly diminish quality of life to such an extent that the intervention would be not beneficial. Carefully-designed, community based clinical trials are likely to be our best bet in determining where to draw the line. ■

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Intraperitoneal Chemotherapy for Ovarian Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *Although prolonged survival was observed in selected patients receiving IP platinum-based therapy, it is not possible to determine the contribution of IP therapy to survival in this study.*

Source: Barakat RR, et al. *J Clin Oncol*. 2002;20: 694-698.

Barakat and colleagues from Memorial Sloan-Kettering Cancer Center reviewed the records of 433 patients who received intraperitoneal (IP) therapy for ovarian cancer between 1984 and 1998; follow-up data were available for 411 patients. IP therapy was provided as consolidation therapy (n = 89), or for treatment of persistent (n = 310) or recurrent (n = 12) disease after surgery and initial systemic therapy; therapy usually consisted of platinum-based combination therapy. The mean age of patients was 52 years (range, 25-76 years). Distribution by stage and grade was as follows: stage I, 7; II, 24; III, 342; IV, 52; not available (NA), 8; and grade 1, 30; 2, 99; and 3, 289; NA, 15. The median survival from initiation of IP therapy by residual disease was none, 8.7 years; microscopic, 4.8 years; less than 1 cm, 3.3 years; more than 1 cm, 1.2 years. In a multivariate analysis, the only significant predictors of long-term survival were grade and size of residual disease at initiation of IP therapy. Barakat et al concluded that,

although prolonged survival was observed in selected patients receiving IP platinum-based therapy, it is not possible to determine the contribution of IP therapy to survival in this study. A relationship between size of disease at the initiation of IP therapy and long-term survival was demonstrated.

COMMENT BY DAVID M. GERSHENSON, MD

Ovarian cancer remains a challenging disease. Despite a high response rate to postoperative chemotherapy after primary cytoreductive surgery—on the order of 80%—most patients with advanced-stage disease will ultimately relapse. Therefore, several strategies have been studied as consolidation therapy for patients in remission and for patients with persistent disease after primary therapy—further systemic chemotherapy, radiation, intraperitoneal chemotherapy (as in this study), and high-dose chemotherapy with stem cell support. The group from Memorial Sloan-Kettering has focused much of their efforts on IP chemotherapy. Several other groups have also studied IP therapy over the past 2 decades or so, and it has found its way into clinical practice in some sectors without any clear information suggesting benefit. Unfortunately, as Barakat et al themselves acknowledge, it is difficult if not impossible to interpret the true value of this approach without conducting a randomized trial. Distinguishing the biologic behavior of the tumor from the influence of the intervention is the challenge in studies such as this. IP therapy has been tested in 3 major randomized trials as part of primary treatment, and the data thus far suggest a slight but real benefit in terms of progression-free survival or overall survival for IP therapy compared with intravenous therapy. Nevertheless, this approach has not been widely embraced, most likely related to the technical difficulties and skepticism regarding the true benefits. ■

Dr. Gershenson is Professor and Chairman, Department of Gynecology, M.D. Anderson Cancer Center, Houston, Tex.

CME Questions

22. Using NCI SEER data coupled with Medicare claims, adjuvant 5-FU chemotherapy for patients aged 65 years and older was shown to be:

a. effective in reducing death rate in patients over the age of 65 years with node-positive colon cancer.
b. effective in reducing death rate in patients with colon cancer metastatic to liver.
c. associated with increased hospitalizations and overall costs form patients with colon cancer.
d. Eeffective in reducing death rates in high performance status colon cancer patients older than 65 years.

23. In order to maximize survival for patients with high-grade glioma, which of the following treatment modalities or combinations of treatment modalities has proven most effective?

a. Cytoreductive surgery
b. Radiation therapy
c. Surgery plus adjuvant chemotherapy
d. Radiation plus immunotherapy
e. Surgery, radiation, and chemotherapy

24. Which of the following statements regarding the Hazard RT/IFN paper is *false*?

a. The mechanism of radiosensitization by IFN remains to be determined.
b. Patients who received IFN with RT developed the same proportion of morbid events as those who received IFN following RT.
c. The IFN Working Group plans to analyze the results of the various soon-to-be-published trials in order to recommend specific doses and schedules of RT/IFN.
d. Brachial plexopathy and soft tissue necrosis were among the unexpected toxicities reported.

25. Examples of primary tumors treated in either Phase II or III trials with RT/IFN are:

a. malignant melanoma and mesothelioma.
b. non-small cell lung cancer and sarcoma.
c. malignant melanoma and cervix cancer.
d. mesothelioma and non-small cell lung cancer.

26. The study of multicentric/multifocal (MCMF) breast cancer by Andea et al suggested that:

a. MC/MF tumors are nearly always infiltrating lobular.
b. MC/MF tumors are nearly always high grade.
c. the risk of lymph node metastasis from MC/MF tumors may be underestimated by the current staging system.
d. MC/MF tumors are almost always two separate primaries rather than clonally related.

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