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ABSTRACT & COMMENTARY

Primary Tumor Resection in Patients Presenting with Metastatic Colorectal Cancer

By William B. Ershler, MD, Editor

SYNOPSIS: In a well-controlled retrospective analysis of patients who presented with metastatic colorectal cancer, primary tumor resection was associated with improved overall survival. By careful multivariate analysis controlling for confounding clinical variables that might result in selection bias (age, performance status, disease burden, etc.), primary tumor resection remained significantly associated with improved survival.

SOURCE: Ahmed S, Leis A, Fields A, et al. Survival impact of surgical resection of primary tumor in patients with stage IV colorectal cancer. Results from a large population-based cohort study. *Cancer* 2014;120:683–691.

Surgical resection of primary colorectal tumors in patients who present with stage IV disease is commonly undertaken,[1] but without firm evidence for benefit in terms of survival.[2-5] Despite a recent meta-analysis of 15 reported observational studies that revealed a 31% reduction in mortality (hazard ratio [HR] = 0.69, 95% CI = 0.61-79) with surgical excision of the primary tumor and an absolute difference in median survival of approximately four months,[6] there remains concern because of potential selection bias. Certainly, younger patients with fewer comorbidities and better functional status would seem more likely to receive surgery, and short of a prospective randomized trial, these concerns will linger. In the current report, Ahmed and colleagues from Saskatchewan attempt to address the selection bias issue by examining a large cohort of newly diagnosed stage IV colorectal cancer (CRC), controlling for several of these potentially confounding variables and assessing survival in those who did or did not receive surgical resection of the primary tumor (SRPT).

This was a large retrospective, population-based cohort study including patients with stage IV CRC diagnosed between 1992 and 2005 in the province of Saskatchewan, Canada. Survival was estimated by using the Kaplan-Meier method and compared by log-rank test. Cox proportional multivariate regression analysis was performed to determine survival benefit of SRPT by controlling for recorded prognostic variables.

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Of a total of 1378 eligible stage IV CRC patients, 944 (68.5%) underwent SRPT. For the whole cohort, the median age was 70 years (range, 22-98 years), the male:female ratio was 1.3:1, and 29.5% had rectal or rectosigmoid tumor (rectal, 20.1%, rectosigmoid, 9.4%). A total of 544 patients (39.5%) were symptomatic, primarily from obstruction (83%), bowel perforation (16%), or major bleeding (10%). Of the total, 1038 (75.3%) had liver metastases and 698 (50.7%) had extrahepatic metastases. Among 698 patients with extrahepatic disease, 217 (31%) had lung metastases, 205 (29.3%) had peritoneal involvement, 31 (4.4%) had bony metastases, and nine (1.3%) patients had documented brain metastases.

Of the 1378 patients, 42.3% received chemotherapy. For those who received SRPT and chemotherapy, the median overall survival was 18.3 months (95% CI = 16.6-20 months), compared to 8.4 months (95% CI = 7.1-9.7 months) for those treated with chemotherapy alone ($p < .0001$).

On univariate analysis, a number of clinicopathological factors were correlated with survival, including ECOG performance status > 1, high CEA, advanced age (poor survival), and use of chemotherapy (better survival). Tests for interaction between surgical resection of primary tumor and age, performance status, CEA level, second-line therapy, or more than one metastatic site were significant. In the proportional hazard model, SRPT was associated with better survival in younger patients, patients with good performance status, normal CEA level, patients treated with second-line therapy, and patients with one metastatic site. By multivariate regression analysis, the use of chemotherapy, SRPT, and surgical resection of metastases were correlated with a favorable survival, whereas older age, poor performance status, low albumin, elevated bilirubin, elevated alkaline phosphatase, anemia, leukocytosis, colonic primary (as opposed to rectal or rectosigmoid), and grade 3 tumor were correlated with inferior survival. After controlling for these clinically important variables, only the interactions between the SRPT and second-line chemotherapy, or more than two metastatic sites, were significant. After adjusting for other important prognostic variables in a Cox proportional multivariate model, the HR for survival with surgical resection of primary tumor was 0.54 (95% CI = 0.48-0.62).

COMMENTARY

Several uncontrolled studies had previously demonstrated a survival benefit for SRPT in the management of stage IV CRC, but it is difficult to generalize from these reports because of selection bias. The current analysis is of a population-based cohort sufficiently large to allow for control of several potentially confounding variables (e.g., age, functional status, comorbidities). The authors found that despite significant differences in the baseline characteristics between the operated and non-operated groups when the known prognostic variables were included in a multivariate model, resection of the primary tumor remained an important prognostic factor. SRPT was associated with 51% relative reduction in mortality after adjustment for age, performance status, comorbid illnesses, chemotherapy, excision of metastases, use of newer chemotherapy regimens, and disease burden. The authors found significant survival differences between the two groups at large (resection versus non-resection), or when examining various subgroups (e.g., those who were asymptomatic or minimally symptomatic at presentation), with the surgical intervention group having significantly better survival in each analysis (range, 7.6-13.6 months).

Clinical oncologists commonly recommend a surgical approach for patients who present with symptomatic disease (i.e., obstruction, perforation, or bleeding), but the current data would suggest that an operative approach should be considered in all, even those who present without symptoms referable to the primary tumor. Under such circumstances, it is unclear why removing the primary tumor would provide survival advantage. It may relate to reduced tumor burden, avoidance of local complications, or an abscopal effect as occasionally observed in patients with renal carcinoma or malignant melanoma. However, despite the large sample size and careful methodology, the current findings are retrospective and need confirmation. In this light, we await the findings from

a randomized study currently underway in the Netherlands (CAIRO 4) examining the role of primary resection in patients presenting with metastatic CRC. ■

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ABSTRACT & COMMENTARY

Contralateral Mastectomy Improves 20-year Survival for BRCA-positive Breast Cancer Patients

By William B. Ershler, MD, Editor

SYNOPSIS: For patients with BRCA-associated breast cancer, it had been previously demonstrated that a second breast cancer occurs in approximately one-third of patients by 15 years after diagnosis, and that this risk was reduced significantly by contralateral mastectomy. In the current observational study, breast cancer mortality at 20 years was shown to be significantly reduced in BRCA-associated breast cancer patients undergoing prophylactic contralateral mastectomy when compared to those treated with unilateral mastectomy alone. Notably, the breast cancer survival benefit associated with contralateral mastectomy was observed in the second decade after initial breast cancer diagnosis.

SOURCE: Metcalfe K, Gershman S, Ghadirian P, et al. Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: Retrospective analysis. *BMJ* 2014;348:g226.

It is now understood that women who carry a germline mutation in either the BRCA1 or BRCA2 gene have a high risk (perhaps 60-70%) for developing breast cancer over their lifetime.[1] Further, once diagnosed with breast cancer, such patients have a high risk of a second primary breast cancer.[2,3] Thus, for patients with hereditary breast cancer, the goals of therapy include the eradication of the primary breast cancer and prevention of a second primary cancer. In discussing breast cancer outcomes, investigators typically focus their attention on the 10-year period after diagnosis, inasmuch as this is when the majority of cancer-related deaths occur. However, a mortality benefit from preventing a second primary breast cancer is unlikely to be apparent in such a short timespan, given that second primary cancers accumulate slowly and for an extended period.[2,4] There remains limited information on the long-term survival experience of women with a BRCA1 or BRCA2 mutation who are treated for breast cancer, and no previous study has examined mortality as it relates to contralateral mastectomy.[5,6] This is highly relevant in North America, where approximately 50% of women with a BRCA mutation-associated breast cancer will undergo mastectomy of the contralateral breast to prevent a second breast cancer,[3] but it has not yet been shown that contralateral mastectomy reduces breast cancer-related mortality. To address this issue, Metcalfe and colleagues reviewed the 20-year survival experience of 390 women with early stage breast cancer, diagnosed from 1975 to 2009, who are known carriers or likely carriers of the BRCA1 or BRCA2 gene and were treated with unilateral or bilateral mastectomy and followed for up to 20 years from diagnosis. Of the 390 patients, 181 had mastectomy of the contralateral breast.

During the follow-up period, 79 women died of breast cancer (18 in the bilateral mastectomy group and 61 in the unilateral mastectomy group). The median follow-up time was 14.3 years (range 0.1-20.0 years). At 20 years, the survival rate for women who had mastectomy of the contralateral breast was 88% (95% CI: 83% to 93%) and 66% for those who did not (59% to 73%). In a multivariable analysis, controlling for age at diagnosis, year of diagnosis, treatment, and other prognostic features, contralateral mastectomy was associated

with a 48% reduction in death from breast cancer (hazard ratio 0.52, 95% confidence interval 0.29 to 0.93; $p = 0.03$). Based on these results, the authors predict that of 100 women treated with contralateral mastectomy, 87 will be alive at 20 years, compared with 66 of 100 women treated with unilateral mastectomy.

COMMENTARY

This study suggests that women who are positive for BRCA mutations and who are treated for stage I or II breast cancer with bilateral mastectomy are less likely to die from breast cancer than women who are treated with unilateral mastectomy. The observed mortality benefit associated with contralateral mastectomy was most apparent in the second decade of follow-up, during which the majority of breast cancer deaths (55%) were from a second primary. This is consistent with the prior observations that for breast cancer patients with a BRCA1 or BRCA2 mutation, the appearance of second malignancies was delayed, on average, 5.7 years.[7] It is also known that BRCA1 or BRCA2 breast cancer patients younger than 50 years are more likely to develop a second breast cancer in the contralateral breast, as are those patients with two or more first-degree relatives with early onset breast cancer.

Thus, in this observational study, women with BRCA-associated breast cancer who were treated with bilateral mastectomy were 48% less likely to die of beast cancer within 20 years of diagnosis than women treated with unilateral mastectomy. The benefit in breast cancer mortality reduction by contralateral mastectomy was most notable in the second decade (35% reduction in the first decade, 80% in the second decade). Yet, the overall number of patients in each of the two study cohorts was relatively small, and additional confirmatory research is necessary. Nonetheless, in light of the accumulated data from this and prior studies, bilateral mastectomy should be discussed as an option, particularly for young BRCA mutation-positive breast cancer patients. ■

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ABSTRACT & COMMENTARY

Addition of Bevacizumab for Newly Diagnosed Glioblastoma

By Bindu Kanapuru, MD

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Dr. Kanapuru reports no financial relationships relevant to this field of study.

SYNOPSIS: In a multicenter, randomized, double-blind, placebo-controlled clinical trial of bevacizumab added to standard temozolomide and radiation therapy for patients with glioblastoma multiforme, progression-free survival but not overall survival was enhanced. Notably, this prolongation of progression-free survival was associated with maintained quality of life and neurocognitive function. This latter important finding is in contrast to that observed in a similar trial, also published in the same *New England Journal of Medicine* issue, indicating bevacizumab-associated decline in quality of life and neurocognitive function. Thus, questions remain regarding when and how this drug should be used in the treatment of glioblastoma.

SOURCE: Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy — temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 2014;370:709-722.

Glioblastoma remains the most common primary brain tumor in adults and is associated with significant morbidity and mortality.[1,2] Currently, the standard of care for patients with newly diagnosed glioblastoma and good performance status includes concurrent radiotherapy and temozolomide, followed by adjuvant temozolomide.[3,4] However, overall survival remains low, and, accordingly, there is great interest in developing and testing new agents. Glioblastomas are highly vascularized tumors that are characterized by the over-expression of vascular endothelial growth factor A (VEGF-A).[5,6] Thus, there has been rationale for examining bevacizumab, an anti-VEGF-A agent, in patients with this tumor. Indeed, early studies have demonstrated a potential role for bevacizumab for patients with both newly diagnosed and recurrent glioblastoma.[7-9]

Chinot and colleagues report the results of the Avastin in Glioblastoma (AVAglio) study, which was conducted at 120 sites in 23 countries and sponsored by F. Hoffmann-La Roche. It was a randomized, placebo-controlled, phase III clinical trial to investigate the effect of the addition of bevacizumab to the standard treatment of radiotherapy and temozolomide in patients with newly diagnosed glioblastoma. Primary endpoints included progression-free survival and overall survival.

Eligible patients were ≥ 18 years of age with newly diagnosed, histologically confirmed supratentorial glioblastoma and a World Health Organization (WHO) performance status of 0-2. Additional inclusion criteria included adequate healing of craniotomy site, stable or decreasing glucocorticoid doses within the 5 days prior to randomization, and satisfactory renal, hepatic, and hematologic function. Exclusion criteria included recent intracranial hemorrhage, prior chemotherapy or immunotherapy for glioblastoma, prior radiotherapy to the brain, and recent intracranial abscess.

Patients were randomly assigned to receive either bevacizumab (10 mg/kg IV every two weeks) or placebo in addition to standard radiotherapy (2 Gy 5 days/week; maximum 60 Gy) and oral temozolomide (75 mg/m^2/day for six weeks). All patients then received a 28-day treatment break, after which they received either maintenance bevacizumab (10 mg/kg IV every 2 weeks) or placebo plus temozolomide (150-200 mg/m^2/day for 5 days) for six 4-week cycles. This was followed by bevacizumab monotherapy (15 mg/kg IV every three weeks) or placebo until disease progression or intolerable adverse effects occurred.

Between June 2009 and March 2011, 921 patients enrolled at 120 sites in 23 countries and were randomly assigned in a 1:1 ratio to bevacizumab (n = 458) or placebo (n = 463). The baseline characteristics were similar in the two groups.

The median progression-free survival was longer in the bevacizumab group than the placebo group (10.6 months vs. 6.2 months). The stratified hazard ratio for progression or death with bevacizumab was 0.64 (95% CI 0.5 to 0.74; $p < 0.001$). This benefit was observed across multiple subgroups, including patients with both methylated and unmethylated MGMT status. However, there were no significant differences in overall survival between the bevacizumab group and the placebo group (72.4% and 66.3% at one year, respectively; $p = 0.049$; 33.9% and 30.1% at 2 years; $p = 0.24$). The median overall survival was 16.8 months in the bevacizumab group and 16.7 months in the placebo group.

Secondary outcome measures included health-related quality of life and performance status, both of which were maintained longer in the bevacizumab group than in the placebo group.

The incidence of grade 3 or higher adverse events was greater in the bevacizumab group than the placebo group (66.8% vs. 51.3%), including those that are often associated with bevacizumab (bleeding, arterial thromboembolic events, hypertension, and proteinuria) (32.5% in the bevacizumab group, vs. 15.8% in the placebo group).

COMMENTARY

Thus, in this large scale, multicenter, randomized, double-blind, placebo-controlled trial, data are presented supporting the addition of bevacizumab to standard radiotherapy and temozolomide for the treatment of newly diagnosed glioblastoma. Although overall survival was not improved, progression-free survival was extended by a median of 4.4 months, and this with maintained quality of life and performance status. Bevacizumab treatment was associated with reduced use of corticosteroids, but was associated with a greater frequency of the adverse events that have been experienced with this drug in other settings (hypertension, proteinuria, and arterial embolism). Of note, there was no demonstrable influence of MGMT status or other prognostic factors (age, performance status) with respect to progression-free survival.

In the same issue of the *New England Journal of Medicine*, Gilbert and colleagues reported the results of the Radiation Therapy Oncology Group (RTOG)

0825 trial, which also investigated bevacizumab for glioblastoma patients using a trial design almost identical to that of the AVAglia study.[10] The RTOG results were also quite similar with respect to absence of observable enhancement of overall survival but enhancement of progression-free survival by 3.4 months. However, the RTOG findings were different in that quality of life and neurocognitive function were not maintained during treatment. This is an important difference because if the AVAglia findings of greater than four months of progression-free survival with maintained function and quality of life is what can be expected by the addition of bevacizumab, then inclusion of this drug in the initial treatment of patients with glioblastoma would be justified. However, looking at the RTOG findings, one might get the impression that the enhanced progression-free survival is countered by increased toxicity and worsening quality of life. Reconciliation of these important treatment outcomes is high priority. In the accompanying editorial,[11] Fine suggests that the investigators from each trial examine the fine details of each study in a comprehensive way and look at issues such as patient characteristics, assessment tools, etc., that might account for the observed differences. That would seem like an excellent suggestion because it remains unclear when and how to use this drug for patients with glioblastoma, and from a consensus understanding, future trials may be designed that will take advantage of this targeted therapy, possibly combined with other agents currently under development. ■

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ABSTRACT & COMMENTARY

Adding to Survival ... Again: Cervical Cancer

By Robert L. Coleman, MD

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

Dr. Coleman reports no financial relationships relevant to this field of study.

This article originally appeared in the March 2014 issue of *OB/GYN Clinical Alert*.

SYNOPSIS: Bevacizumab added to chemotherapy, particularly paclitaxel and cisplatin, was efficacious in all response outcomes (objective response, progression-free survival, and overall survival) without diminution in quality of life or unacceptable toxicity.

Source: Tewari KS, et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med* 2014;370:734-743.

Patients with metastatic and recurrent cervix cancer typically receive platinum-based therapy in an attempt to control tumor growth. Recently, anti-vascular endothelial growth factor (VEGF) targeted therapies have demonstrated single agent activity in this disease. As use of platinum-based chemoradiation has increased in this setting, expectations of response to platinum at the time of recurrence has decreased, therefore questioning efficacy. This has resulted in an ushering of clinical studies to evaluate the efficacy of non-platinum regimens. GOG-240 was a 2 x 2

factorial designed trial, randomly assigning 452 patients to chemotherapy (paclitaxel/cisplatin or paclitaxel/topotectan) with or without bevacizumab at a dose of 15 mg/kg. Cisplatin was dosed at 50 mg/m^2, with paclitaxel at a dose of 135 or 175 mg/m^2; and topotecan at a dose of 0.75 mg/m^2, days 1 to 3, plus paclitaxel at a dose of 175 mg/m^2 on day 1. Cycles were repeated every 21 days until disease progression, the development of unacceptable toxic effects, or a complete response was documented. The primary endpoint was overall survival; a reduction of 30% in the hazard ratio for death was considered clinically important. The treatment cohorts were well balanced with respect to age, histologic findings, performance status, previous use or non-use of a radiosensitizing platinum agent, and disease status. In an interim evaluation, topotecan-paclitaxel was not found to be superior to cisplatin-paclitaxel (hazard ratio [HR] for death, 1.20). After collapsing the chemotherapy regimens for analysis, the addition of bevacizumab to chemotherapy was associated with increased overall survival (17.0 months vs. 13.3 months: HR, 0.71; 95% confidence interval [CI], 0.54-0.95; $p = 0.004$ in a one-sided test), increased progression-free survival (8.2 months vs. 5.9 months: HR, 0.67; 95% CI, 0.54-0.82; two sided $p = 0.002$), and higher response rates (48% vs. 36%, $p = 0.008$). Bevacizumab, as compared with chemotherapy alone, was associated with an increased incidence of hypertension of grade 2 or higher (25% vs. 2%), thromboembolic events of grade 3 or higher (8% vs. 1%), and gastrointestinal fistulas of grade 3 or higher (3% vs. 0%). The authors concluded that the addition of bevacizumab to combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer was associated with an improvement of 3.7 months in median overall survival.

COMMENTARY

Cancer of the uterine cervix is the second most common cancer afflicting women worldwide and is a major cause of preventable mortality. It also disproportionately impacts underserved and under-resourced populations. However, about half of cervix cancer cases diagnosed in the United States each year are at advanced stages or metastatic at presentation. Primary treatment with chemoradiotherapy provides modest tumor control for many, but those women whose tumors are not amenable to curative intervention are left with few therapeutic options. The investigative story of chemotherapy for metastatic and recurrent cervix cancer has been methodical and deliberative, moving from non-platinum agents to platinum single agents to platinum-doublets and triplets and finally to the introduction of chemotherapy with anti-angiogenesis agents.[1] The progress, albeit slow, has been significant, moving anticipated overall survival 25 years ago of approximately 6 months to now nearly 18 months. This trial represents a significant advance forward and breaks a therapeutic ceiling reached in the previous GOG study (protocol 204), which was unable to identify a survival gain among any of the four platinum-based doublets tested.[2]

Many relevant observations in this trial add to the credibility of the overall conclusions. First, the control arm's performance was as expected; both the platinum and non-platinum-based doublets were associated with progression-free survival and response as anticipated and consistent with previous contemporary (since 1999) trials. This suggests a stable patient population, particularly with regard to the proportion of patients exposed to prior platinum-based chemoradiation (70% in the current trial). A previous phase III trial of single-agent cisplatin vs. cisplatin and topotecan demonstrated substantially lower response rates to single-agent platinum when platinum-based chemoradiation was used in prior therapy.[3,4] Second, biological and clinical rationale supports the use of anti-VEGF based therapy. The GOG and others have demonstrated that VEGF targeting as a single agent has clinical activity in recurrent cervix cancer.[5] Biologically, de-repression of E6/E7 leads to increased VEGF expression and vulnerability to anti-VEGF based therapy. Third, the evaluated outcome variables were enhanced in the experimental cohort (response, progression-free survival, and overall survival) and were favorably impacted by the addition of bevacizumab, including consistent findings for objective response regardless of measurable disease within a radiated field. It previously has been observed in many trials that metastatic extrapelvic disease has nearly doubled the response rate of intrapelvic (and infield) disease. However, the current trial demonstrated equal efficacy in the experimental arm. Finally, quality of life was not hampered by the increase in (expected) toxicity.

With the publication of this study, it is likely that a new standard will be supported for women with metastatic and recurrent cancer of the cervix by the FDA. However, the greatest burden of disease resides in areas of the world where this expen-

sive therapy is not within reach. Further work and drug availability will be needed to continue to reduce the impact of this disease, which globally wreaks havoc on young women and their families. ■

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- discuss the most recent information regarding diagnosis and treatment of various types of cancer;
- describe current prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- describe new advances in the field of oncology.

Continuing Education Questions

1. In the Canadian retrospective review of surgical resection of primary tumor in patients presenting with metastatic colorectal cancer, improved overall survival for those receiving surgery compared with those not receiving surgery was apparent in which groups?

a. those who were asymptomatic or minimally symptomatic at presentation.
b. those with normal CEA titers
c. those who are going to receive postoperative chemotherapy
d. those with ECOG PS of 0 or 1
e. all of the above

2. In patients with BRCA-associated breast cancer prophylactic contralateral mastectomy, the current report by Metcalfe and colleagues demonstrated:

a. a reduction in breast cancer-associated mortality that was greatest in the first 5 years after diagnosis
b. a reduction in breast cancer-associated mortality that was greatest in the second decade after initial diagnosis
c. a reduction in breast cancer incidence in the contralateral breast but no impact on overall survival at 20 years after diagnosis
d. no reduction in either second malignancy incidence or breast cancer survival at 20 years after diagnosis

3. Data from the AVAglia trial indicates that the addition of bevacizumab to standard temozolomide/radiation therapy may be exptected to:

a. enhance median overall survival by approximately 6 months
b. enhance median progression-free survival by approximately 4 months
c. have no effect on overall or progression-free survival
d. decrease overall survival

[IN FUTURE ISSUES]

Antihypertensive treatments and the prevention of colorectal cancer