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Prediction and Promise: *KRAS* and Colorectal Cancer

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Cancer remains a major cause of death and disability in the developed world. As we enter the new millennium, the promise of improved cancer biology knowledge leading to new cancer treatments is being realized. We want to be able to offer these breakthrough treatments to patients who will benefit from them. Moreover, we would like to avoid initiating therapy in patients who have little chance of responding, and hence eliminate the toxicity of ineffective therapy and enable other treatment approaches to be pursued. Up until recently, however, there were no such predictors of response and benefit to guide our management approach to advanced colorectal cancer. Chemotherapy drugs with or without bevacizumab were tried and changed when treatment failure was observed. The results of the CO.17 trial have helped to change the treatment paradigm for metastatic colorectal cancer when using monoclonal antibodies that target the epidermal growth factor receptor (EGFR).¹

Why did we look at *KRAS*?

Study CO.17 was initiated by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) in collaboration with the Australasian Gastro-Intestinal Trials Group (AGITG). This multicen-

ter, prospective, open-label, randomized, phase 3 trial compared cetuximab plus best supportive care (BSC) with BSC alone in patients with pretreated metastatic colorectal carcinoma.² All the patients had received previous chemotherapy, and the treating physician considered that further chemotherapy would not help the patient. The only remaining standard therapy for patients entering this study, as recommended by the investigator, was BSC. Patients in the cetuximab arm received the agent as a once-per-week intravenous infusion.

LEARNING OBJECTIVES

After completing this activity, the reader should be better able to:

- Explain the rationale for studying the effect of *KRAS* mutations in patients with metastatic colorectal cancer
- Discuss how *KRAS* mutations affect response to epidermal growth factor receptor (EGFR) inhibitor therapy in patients with metastatic colorectal cancer
- Describe common toxicities associated with use of anti-EGFR monoclonal antibodies and measures that can be taken to prevent and manage them
- Explain how use of biomarkers such as *KRAS* mutations to select therapy can lead to more cost-effective treatment of patients with cancer

TARGET AUDIENCE

Advanced practice nurses, registered nurses, and other interested healthcare professionals, especially those caring for cancer patients

COST

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ter, prospective, open-label, randomized, phase 3 trial compared cetuximab plus best supportive care (BSC) with BSC alone in patients with pretreated metastatic colorectal carcinoma.² All the patients had received previous chemotherapy, and the treating physician considered that further chemotherapy would not help the patient. The only remaining standard therapy for patients entering this study, as recommended by the investigator, was BSC. Patients in the cetuximab arm received the agent as a once-per-week intravenous infusion.

The trial demonstrated that cetuximab when used as a single agent improves overall survival and prolongs progression-free survival in patients with colorectal cancer after failure of chemotherapy, but the majority of patients did not respond to cetuximab in this setting, with more than 50% of patients showing disease progression at the time of the first disease-response assessment.²

Cetuximab is a monoclonal antibody that binds to the EGFR with high affinity and inhibits the subsequent activation of downstream signaling pathways.³ Kirsten rat sarcoma (*KRAS*), a small protein downstream of EGFR, is an essential component of the EGFR signaling cascade and may represent a bottleneck in the pathway.⁴ Mutations in the *KRAS* gene can lead to constitutive activation of the pathway, and this may render inhibitors of components of the cascade upstream of *KRAS*

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ineffective. *KRAS* mutations, therefore, may predict for lack of efficacy of inhibitors that target the EGFR.⁵ *KRAS* gene mutations occur early in the stages of carcinogenesis, as the colorectal adenoma progresses to develop into a carcinoma.⁶ *KRAS* mutations are found in 30% to 50% of colorectal cancers.⁷⁻¹⁰

Examination of tumor tissue is crucial

For the current study, colorectal cancer tumor samples were collected from 394 patients involved in the CO.17 trial, representing 69% of all the patients in that trial. Mutation analysis for the *KRAS* gene was performed by direct gene sequencing to examine the tumor DNA in detail and look specifically at the DNA that codes for the *KRAS* gene. We effectively divided the tumor samples into two groups, those that exhibited *KRAS* mutations and those that did not. *KRAS* genes without mutations are called "wild type." We found that 42% of the tumor samples examined exhibited mutations of the *KRAS* gene, and this frequency is in keeping with previously published reports. We then set out to see whether *KRAS* mutation status was associated with differences in patient outcome.

The results: *KRAS* does matter

We observed a significant difference in survival times, but only for one of the *KRAS* groups. Overall survival was almost doubled for patients treated with cetuximab if the tumor did not have a *KRAS* mutation (ie, the *KRAS* wild-type subgroup). In the *KRAS* wild-type subgroup, median survival was 9.5 months in those receiving cetuximab and 4.8 months with BSC alone (Figure). Similarly, progression-free survival was also prolonged with cetuximab therapy in patients with *KRAS* wild-type tumors (3.7 months vs 1.9 months). In contrast, the survival time was not prolonged with cetuximab treatment in patients whose tumors had *KRAS* mutations. For those patients, median survival was the same in the cetuximab-treated and BSC arms, 4.5 and 4.6 months, respectively. Progression-free survival was also the same in the two arms for patients with *KRAS*-mutant tumors. *KRAS* mutation status was found to be correlated with overall survival, progression-free survival, and radiologic response. Quality-of-life analysis also demonstrated that patients with *KRAS* wild-type tumors derived the greatest benefit.

Overall, the benefit obtained with cetuximab in the setting of advanced colorectal cancer previously treated with chemotherapy was isolated to patients with tumors that do not exhibit *KRAS* gene mutations. No benefit

was observed from using cetuximab in patients whose tumors had *KRAS* mutations. This correlation of *KRAS* mutation status and treatment effect has also been observed in other published retrospective series.¹⁰⁻¹³

Is *KRAS* also a prognostic factor?

The presence of a *KRAS* mutation may predispose to more aggressive biological behavior of the cancer, but the prognostic significance of *KRAS* mutations has varied in reported series.^{7-9,14,15} In our study, we were able to examine the survival of patients who did not receive any cancer treatment, because these patients were in the BSC arm. In this way, we could examine the impact of *KRAS* on survival without having to consider a possible effect of treatment. We did not observe that the presence of a *KRAS* mutation predicts for a more aggressive cancer and a poorer prognosis.

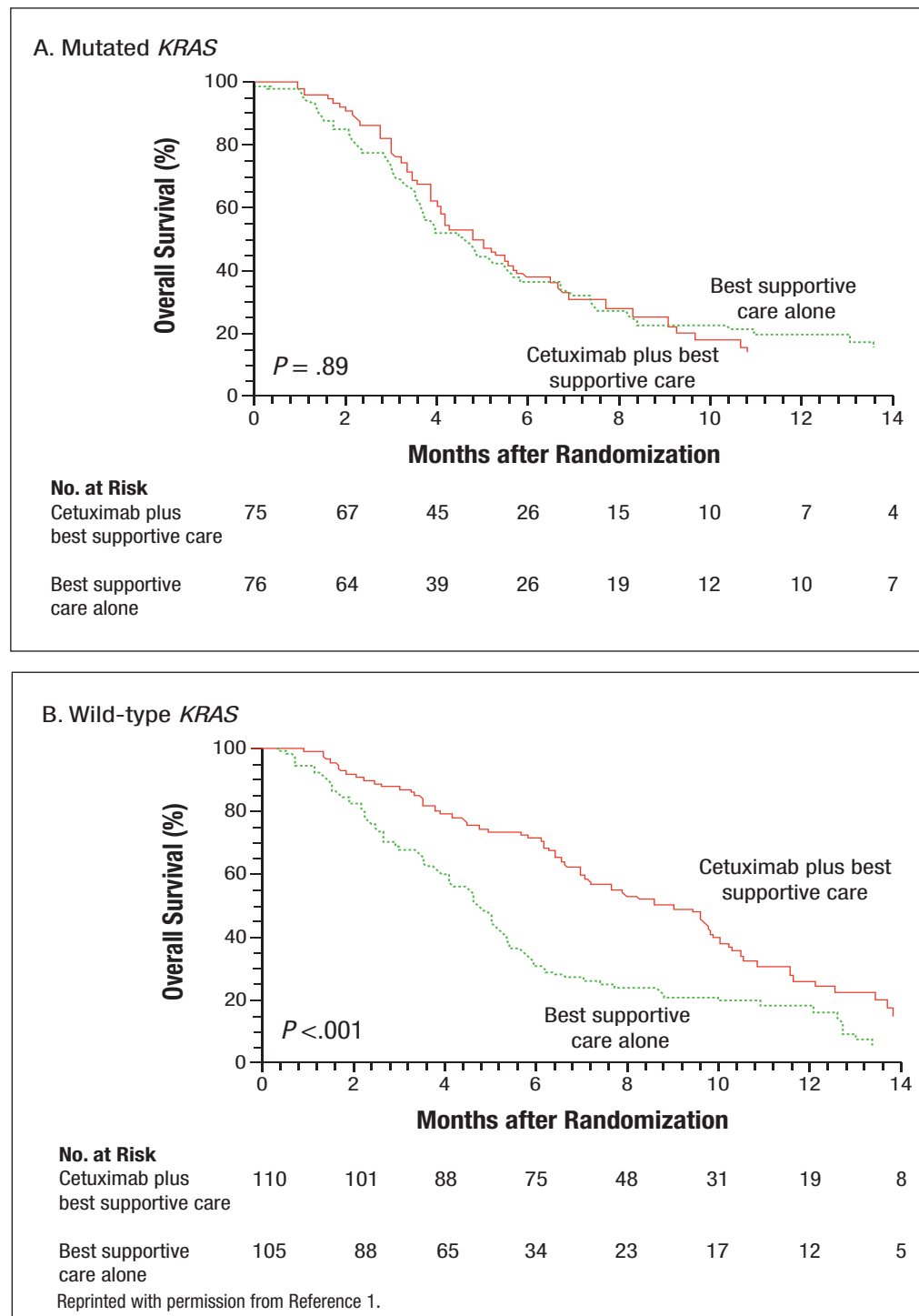
We found no difference in the survival of patients according to *KRAS* mutation status in the BSC group. Median survival was 4.6 months in patients with *KRAS*-mutant tumors on BSC and 4.8 months in those with *KRAS* wild-type tumors on BSC, with 1-year survival of 19.6% and 20.1%, respectively. This analysis provides the best assessment of the influence of *KRAS* mutation status on survival without the effect of another variable such as treatment with cetuximab.

Where to now?

Although *KRAS* mutations may represent a common genetic aberration involved in cancer development, other gene mutations can also lead to unrestricted cancer cell growth. Some of these are already being examined, including loss of *PTEN* activity,¹⁶ gene expression of the EGFR ligands amphiregulin and epiregulin,¹⁷ and *PI3KCA* mutations.¹⁸

Over the past decade, there has been a paradigm shift in the way we manage patients with advanced colorectal cancer. Multiagent chemotherapy and multiple lines of therapy are now part of optimal treatment strategies. Antiangiogenic therapy has contributed further to improving the outcome of such patients, particularly in progression-free survival, with an associated prolongation of overall survival. The benefit of antiangiogenic therapy has been observed when bevacizumab is used as

Figure. Kaplan-Meier Curves for Overall Survival According to Treatment



part of either first- or second-line therapy. EGFR-directed therapy, particularly using cetuximab and panitumumab, has also prolonged survival and progression-free survival, but this prolongation is restricted to patients with *KRAS* wild-type tumors.

In the future, cost-benefit analysis may become a major factor in deciding on wider availability of these agents. Cetuximab is a relatively expensive pharmacologic therapy. The cost-effectiveness of this treatment approach improves when the treatment can be delivered to those patients with a higher chance of benefiting. The major challenge is the identification of appropriate predictors of response to

these drugs. Low response rates, short survival times, and relatively expensive new drugs have provided an understandable impetus to discover predictors of benefit from therapy. Avoiding therapy in patients who have little chance of responding can help to eliminate toxicity of ineffective therapy and allow other treatment approaches to be pursued.

The results of the CO.17 study have identified a biomarker that can effectively exclude a significant proportion of patients with colorectal cancer, approximately 40% with tumors that have *KRAS* mutations, from a therapy

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that has very little prospect of providing a benefit. An accurate and reliable biomarker that allows selection of a subpopulation of patients with advanced colorectal cancer who will benefit from new therapies represents a significant advance in the clinical management of this disease. *KRAS* has now been proved to be such a biomarker and should be routinely examined and used to select patients for treatment with EGFR-

directed monoclonal antibodies such as cetuximab and panitumumab.

The ideal predictive biomarker is one that identifies all of those patients who will benefit from therapy before initiation of treatment, and excludes the patients who will not respond. Although *KRAS* has a significant predictive effect, it is not perfect. In our study, some patients with *KRAS* wild-type tumors did not respond to cetux-

imab and had rapid cancer progression. Other prognostic and predictive variables that can be reliably and easily measured need to be identified. ●

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COMMENTARY

KRAS and Colorectal Cancer: A Pharmacist's Perspective

BY BETTY M. CHAN, PHARM.D, BCOP

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Recent advances with chemotherapeutic agents (ie, oxaliplatin, irinotecan) and targeted biologic agents (ie, anti-epidermal growth factor receptors [EGFRs] cetuximab, panitumumab; anti-vascular endothelial growth factor bevacizumab) have greatly expanded our treatment options for patients with colorectal cancer. Recent findings on use of Kirsten rat sarcoma (*KRAS*) mutational status to predict response to anti-EGFR monoclonal antibodies further demonstrated our need to streamline patient selection to those likely to derive the greatest benefit (ie, those with *KRAS* wild-type tumors only) from treatment so as to minimize treatment toxicities and provide cost-effective treatment.

In the article by Karapetis, the author reported that results from the CO.17 trial have helped change the treatment paradigm for metastatic colorectal cancer. In the study, overall survival and progression-free survival were significantly improved in patients with *KRAS* wild-type tumors who received treatment with cetuximab compared with best supportive care.¹ In addition to the findings reported by Karapetis and colleagues, several other recent publications have reported greater improvement in response rates, progression-free survival, and overall survival when an anti-EGFR monoclonal antibody (ie, cetuximab or panitumumab) is used as monotherapy or in combination with chemotherapy agents in patients with advanced colorectal cancer who have *KRAS* wild-type tumors.²⁻⁶

Although treatment with an anti-EGFR monoclonal antibody (cetuximab or panitumumab) is much better tolerated by patients compared with chemotherapy, most patients receiving treatment do experience toxicities.^{7,8} As with other monoclonal antibodies, infusion-related symptoms include fever, chills, urticaria, flushing, fatigue, headache, bronchospasm, dyspnea, angioedema, and hypotension. Incidence rates are higher in patients receiving cetuximab, a chimeric monoclonal antibody, than in those receiving panitumumab, a fully humanized IgG2 monoclonal antibody. Premedication is needed in patients before treatment with cetuximab because the incidence of infusion reactions is higher with the first infusion (40%-50% reported) than with subsequent infusions (<1%). Close monitoring for all infusions is recommended, however, to minimize infusion

reactions and to provide supportive care if infusion reactions develop.^{7,8}

Skin toxicity, although often considered a surrogate marker for clinical activity, is, nevertheless, another common toxicity associated with anti-EGFR monoclonal antibodies. Commonly observed skin toxicities include acneiform skin rash with papulopustular eruption on the face and upper trunk, dry skin with pustular eruptions, and pruritus. Management includes educating patients to avoid sun exposure, which may exacerbate skin reactions, and to apply a para-aminobenzoic acid-free sunscreen with a sun-protection factor of 15 or higher before sun exposure. Dosage adjustment may be necessary, depending on the severity of skin toxicity. Topical antibiotics with clindamycin or its derivatives (ie, clindamycin phosphate 1% gel for isolated lesions and clindamycin phosphate 1% lotion for scattered lesions) can be used for mild skin toxicity. For moderate-to-severe skin toxicity, systemic oral antibiotics (ie, minocycline or doxycycline 100 mg orally twice a day for 10-14 days) can be used. For dry skin, applying emollient twice a day may provide relief of symptoms. Pruritus can be managed with diphenhydramine or hydroxyzine 25 mg to 50 mg orally every 6 hours as needed.⁹⁻¹²

Electrolyte abnormalities such as hypomagnesemia and hypocalcemia have also been reported. Hypomagnesemia has been observed as early as 3 weeks into treatment with cetuximab.^{13,14} Close monitoring of magnesium and calcium levels before treatment is recommended, providing electrolytes supplementation as needed.

Pulmonary toxicity including interstitial lung disease, although rare (<1%), has been reported with anti-EGFR monoclonal antibodies. Patients with acute-onset or worsening pulmonary symptoms (eg, increased cough, dyspnea, and pulmonary infiltrates) must be carefully monitored, and holding or discontinuing treatment may be necessary in patients with pulmonary toxicities.^{7,8}

Generalized malaise and asthenia have been observed (with cetuximab more than panitumumab).^{7,8} Paronychia inflammation and swelling of lateral nail folds of fingers and toes has also been reported in patients receiving treatment for a prolonged period of time. Management options include topical antibiotics or topical corticosteroids.^{11,12}

Although toxicities associated with anti-EGFR monoclonal antibody therapy are generally mild

and manageable, frequent assessment and close monitoring are still required to minimize toxicities and patient discomfort. Nurses and pharmacists can assist with the assessment and monitoring of these toxicities, and develop management guidelines in their institution for the treatment of skin toxicities and the management of hypomagnesemia.

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COMMENTARY

KRAS and Colorectal Cancer: A Nurse's Perspective

BY SANDRA E. KURTIN, RN, MS, AOCN, ANP-C

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The search for the silver bullet in cancer treatment has long been the elusive coup de grâce. We envision a time when treatments are selected based on clearly defined targets with little or no collateral damage. With the advent of molecular profiling and advanced tissue analysis, which can identify key components of signaling pathways, we are moving toward this future.

Signaling pathways are present in both normal and abnormal cellular function and provide attractive targets for manipulation of abnormal pathways. Inhibition of the epidermal growth factor receptor (EGFR) and its downstream pathways using targeted monoclonal antibodies has provided a unique treatment strategy in patients with colorectal cancer. EGFR upregulation is present in 25% to 80% of colorectal cancers, making it an attractive target.¹ Blocking EGFR pathways may interrupt the pathologic effects of EGFR overexpression, including cell cycle progression, apoptosis, angiogenesis, tumor cell motility, and metastasis.²

Recently, the role of the Ras/Raf/mitogen-activated protein kinase pathway has elucidated the critical role of the Ras oncogene in colorectal tumorigenesis and response to EGFR-inhibiting agents.³ *KRAS*, an intracellular signal transducer, is the gene that codes for the Ras signaling pathway. Mutations in *KRAS* are present in approximately 40% of colorectal tumors, with a high concordance (90%) between primary and metastatic sites at the time of diagnosis.⁴ *KRAS* mutations are thought to alter protein activity, leading to unregulated cellular proliferation and malignant transformation.⁵ *KRAS* mutations in codon 12 and 13 have been extensively analyzed in phase 2 and 3 clinical trials using EGFR inhibitors either as monotherapy or in combination with other agents.^{3,6-8} In all studies, patients with *KRAS* mutations did not derive benefit from treatment with EGFR-inhibiting monoclonal antibodies (cetuximab and panitumumab). Despite the retrospective and

subset-analysis techniques used in the majority of these studies, the strength of the data has been largely undisputed by clinicians.

As a result of these studies, the American Society of Clinical Oncology (ASCO) issued a Provisional Clinical Opinion⁷: "Based on systematic reviews of the relevant literature, all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for *KRAS* mutations in a [Clinical Laboratory Improvement Amendments] CLIA-accredited laboratory, according to ASCO. If *KRAS* mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as a part of their treatment." Importantly, the group did offer qualifications that *KRAS* mutational status has not been validated as a prognostic factor in the analyzed studies. [Editor's note: On July 17, 2009, the US Food and Drug Administration approved class labeling changes to cetuximab and panitumumab, noting that these agents are not recommended for treatment of colorectal cancer with *KRAS* mutations in codons 12 and 13.]

These findings have changed the treatment paradigm for colorectal cancer, mandating comprehensive and accurate tissue testing at the time of diagnosis for all newly diagnosed colorectal cancers, testing of existing tissue blocks for those who have recurrent or progressive disease when testing has not already been done, and effectively eliminating a treatment option for a large number of patients with metastatic disease who test positive for the *KRAS* mutation.

The mandate for clinicians and researchers is clear: We must work diligently to enroll patients in clinical trials that may provide new treatment options for this disease. Proactive and aggressive management of disease and treatment-related toxicities is essential to optimal clinical outcomes and necessary to avoid the elimination of future treatment options because of residual toxicities or secondary organ damage. This

applies to effective management of EGFR inhibitor-associated toxicities for those patients who are fortunate enough to have *KRAS* wild-type tumors. Strategies for evaluation of treatment response and grading of toxicities will need to be refined to avoid premature discontinuation of therapies. Analysis of the sequencing of the seven commonly used US Food and Drug Administration-approved agents for this disease may be required to achieve optimal outcomes with the limited treatment options for metastatic colorectal cancer. Personalized medicine through molecularly driven treatment selection is definitely a double-edged sword.

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