

Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer

TO THE EDITOR: Cunningham et al. (Jan. 3 issue)¹ state that capecitabine and oxaliplatin are equivalent to fluorouracil and cisplatin in esophagogastric cancer. One disadvantage of their study is that patients with squamous-cell carcinoma were not excluded. Furthermore, it seems that combinations of capecitabine and oxaliplatin are not less toxic or more effective but their cost is 5 to 10 times that of therapy with epirubicin, cisplatin, and fluorouracil (ECF). Moreover, peripheral neuropathy occurs more frequently with oxaliplatin.^{2,3} We therefore see no better profile for capecitabine and oxaliplatin in patients with advanced esophagogastric cancer.

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1. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;358:36-46.
2. Mauer AM, Kraut EH, Krauss SA, et al. Phase II trial of oxaliplatin, leucovorin and fluorouracil in patients with advanced carcinoma of the esophagus. *Ann Oncol* 2005;16:1320-5.
3. Kannarkat G, Lasher EE, Schiff D. Neurologic complications of chemotherapy agents. *Curr Opin Neurol* 2007;20:719-25.

THE AUTHORS REPLY: In our study, the oral pro-drug capecitabine was as effective as fluorouracil, with a trend toward superiority and with similar toxicity. Patients with cancer often prefer oral alternatives to intravenous treatments, provided that efficacy is maintained.¹ The convenience for patients is a key consideration. During ECF therapy, fluorouracil is administered continuously throughout treatment (up to 6 months) through a central venous access device and an ambulatory

pump requiring either community or hospital-based support. Such therapy is associated with morbidity, (i.e., infection, pain, thrombosis, and hospitalization).

As compared with cisplatin, oxaliplatin was associated with less thromboembolism, renal toxicity, alopecia, and neutropenia and required no additional hydration (considerably shortening the duration of outpatient visits). Oxaliplatin is widely used in colorectal cancer, in which peripheral neuropathy is managed by dose adjustment. Among patients who received epirubicin, oxaliplatin, and capecitabine (EOX), the median overall survival (11.2 months) was the longest period observed in our trials evaluating ECF in esophagogastric cancer, in which patients with advanced squamous-cell cancer accounted for less than 10% of 1002 patients.^{2,3}

Incremental treatment-related costs will probably be less than those suggested by Bölke et al., since oxaliplatin is available as a generic drug in Europe. Drug costs may be offset by ECF-related nondrug costs, inconvenience to patients, and toxicity.

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1. Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol* 1997;15:110-5.
2. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997;15:261-7.
3. Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol* 2002;20:1996-2004.

The *HIF2A* Gene in Familial Erythrocytosis

TO THE EDITOR: Percy et al. (Jan. 10 issue)¹ uncovered a mutation within the hypoxia-inducible factor 2 α (*HIF2A*) gene as a cause of attenuated HIF-2 α degradation and increased erythropoietin

production in patients with familial erythrocytosis. This is an exciting observation, since studies on the relative contribution of HIF-1 α and HIF-2 α to hypoxia-driven gene expression are areas of

intense investigation.^{2,3} A recent study of erythropoiesis in mice with tissue-specific deletion of *Hif1a* or *Hif2a* showed that hepatic erythropoietin production is preferentially regulated by Hif-2 α .⁴ In contrast, renal erythropoietin appears to be regulated predominantly by Hif-1 α .⁵ Do Percy et al. know whether familial erythrocytosis that is caused by a mutation of *HIF2A* increases erythropoiesis predominantly in the liver or the kidney?

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1. Percy MJ, Furlow PW, Lucas GS, et al. A gain-of-function mutation in the *HIF2A* gene in familial erythrocytosis. *N Engl J Med* 2008;358:162-8.
2. Ratcliffe PJ. HIF-1 and HIF-2: working alone or together in hypoxia? *J Clin Invest* 2007;117:862-5.
3. Semenza GL. Life with oxygen. *Science* 2007;318:62-4.
4. Rankin EB, Biju MP, Liu Q, et al. Hypoxia-inducible factor-2 (HIF-2) regulates hepatic erythropoietin in vivo. *J Clin Invest* 2007;117:1068-77.
5. Semenza GL. Regulation of mammalian O₂ homeostasis by hypoxia-inducible factor 1. *Annu Rev Cell Dev Biol* 1999;15:551-78.

TO THE EDITOR: Percy et al. conclude that HIF-2 α may be central to the regulation of erythropoietin levels, but HIF-1 α was identified by its binding to a 3' hypoxia-responsive element of the erythropoietin gene in the kidney,¹ and severe anemia develops after nephrectomy. In contrast, the erythropoietin gene in the liver is regulated by upstream nucleotide sequences,² and the liver produces only about 10 to 20% of the total erythropoietin. Alternative explanations for the phenotype described by Percy et al. are autonomous generation of erythropoietin by the liver (possibly with suppressed renal production of erythropoietin) or stimulation of transcription of the erythropoietin gene in the kidney and liver by the increased nitric oxide that accompanies the defect.³

The authors report that they increased the rate of phlebotomy in response to deep-vein thrombosis in the index patient. However, thrombosis that is associated with increased HIF-1 α expression might be related to the altered expression of target genes that influence coagulation pathways⁴ rather than to polycythemia itself. Iron deficiency that is induced by phlebotomy could conceivably further increase HIF-1 α levels⁵ and the risk of thrombosis.

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1. Hirota K, Semenza GL. Regulation of angiogenesis by hypoxia-inducible factor 1. *Crit Rev Oncol Hematol* 2006;59:15-26.
2. Semenza GL, Koury ST, Neifelt MK, Gearhart JD, Antonarakis SE. Cell-type-specific and hypoxia-inducible expression of the human erythropoietin gene in transgenic mice. *Proc Natl Acad Sci U S A* 1991;88:8725-9.
3. Johnson RS. Tissue-specific effects of HIF-1 loss of function. Presented at the Keystone Symposia on Molecular, Cellular, Physiological, and Pathogenic Responses to Hypoxia, Vancouver, BC, Canada, January 15–20, 2008.
4. Gordeuk VR, Prchal JT. Vascular complications in Chuvash polycythemia. *Semin Thromb Hemost* 2006;32:289-94.
5. Peyssonnaud C, Zinkernagel AS, Schuepbach RA, et al. Regulation of iron homeostasis by the hypoxia-inducible transcription factors (HIFs). *J Clin Invest* 2007;117:1926-32.

TO THE EDITOR: Percy et al. report an example of familial polycythemia, with inappropriately high erythropoietin levels due to a mutation of the gene that encodes HIF-2 α . They conclude that this transcription factor, not HIF-1 α , is the primary cause of the erythrocytosis in their patients. However, no analysis of the *HIF1A* gene was reported. We have investigated both *HIF1A* and *HIF2A* in 125 patients with familial erythrocytosis. We found that none of the patients had alterations in *HIF1A* and only one patient had a mutation of *HIF2A*. The change in the latter gene involved the same codon of *HIF2A* that was found by Percy et al., but it resulted in a different residue change (Gly537Arg). The absence of *HIF1A* mutations and the occurrence of a novel *HIF2A* mutation support the authors' conclusion that HIF-2 α plays a pivotal role in the control of expression of the erythropoietin gene.

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THE AUTHORS REPLY: Eltzhig et al. and Prchal and Gordeuk raise the issue of the source of erythropoietin in the family members with erythrocytosis whom we studied. Although we do not have direct evidence of the source in these patients, we believe that studies in genetically modified mice are relevant. Liver-specific deletion of

Hif2 α indicates that this isoform regulates erythropoietin production in the adult mouse liver.¹ To the best of our knowledge, the corresponding cell-specific deletion experiment for erythropoietin-producing cells of the kidney has not been performed. However, Gruber and colleagues induced acute global deletion of both *Hif1 α* and *Hif2 α* in mice and found that the deletion of *Hif2 α* , but not *Hif1 α* , results in anemia.² If *Hif1 α* were the central isoform or merely a redundant isoform in the kidney, one might expect that *Hif1 α* deletion would result in anemia or, at least, that the *Hif2 α* deletion would not cause anemia. The observation that the *Hif2 α* deletion does cause anemia indicates that this isoform is the critical regulator of erythropoietin. The point regarding the cause of the deep venous thrombosis is well taken and will require further investigation into the question of whether it might be mediated by HIF target genes.

Perrotta and Della Ragione state that they did not find evidence of any *HIF1A* mutation in their patients with erythrocytosis, a finding that is

consistent with the results of a study we reported previously,³ but they did note an additional case of an erythrocytosis-associated mutation in the *HIF2A* gene. This observation is a further indication of the role played by HIF-2 α in regulating erythropoietin in idiopathic erythrocytosis.

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1. Rankin EB, Biju MP, Liu Q, et al. Hypoxia-inducible factor-2 (HIF-2) regulates hepatic erythropoietin in vivo. *J Clin Invest* 2007;117:1068-77.
2. Gruber M, Hu CJ, Johnson RS, Brown EJ, Keith B, Simon MC. Acute postnatal ablation of *Hif2 α* results in anemia. *Proc Natl Acad Sci U S A* 2007;104:2301-6.
3. Percy MJ, Mooney SM, McMullin MF, Flores A, Lappin TR, Lee FS. A common polymorphism in the oxygen-dependent degradation (ODD) domain of hypoxia inducible factor-1 α (HIF-1 α) does not impair Pro-564 hydroxylation. *Mol Cancer* 2003;2:31.

Long-QT Syndrome

TO THE EDITOR: In his discussion of the Clinical Practice vignette involving a fatal arrhythmic event in a child with the long-QT syndrome, Roden (Jan. 10 issue)¹ emphasizes the importance of rigorously screening family members in order to provide an optimal prevention strategy. The author recommends that affected persons not participate in competitive sports; he also mentions the benefit of beta-blocker therapy in these patients and the use of implantable cardiac defibrillators in the highest-risk cases. However, the current recommendations consider “lifestyle modifications,” defined by the contraindication of competitive sports activity and of all drugs known to prolong the QT interval, as a class I recommendation (level of evidence B).² According to such recommendations, education of these patients about the risk associated with certain drugs must be clearly integrated into the strategy of fatal-arrhythmia prevention. All these drugs are listed and regularly updated in the International Registry for Drug-Induced Arrhythmias (www.qtdrugs.org).

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1. Roden DM. Long-QT syndrome. *N Engl J Med* 2008;358:169-76.
2. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;114(10):e385-e484.

TO THE EDITOR: Effective therapies exist for the long-QT syndrome. The use of beta-blockers should be viewed as the mainstay of therapy, as noted in the Clinical Practice article. Although there is a reduction in cardiovascular events among