The Cost and Value of Anti-Epidermal Growth Factor Receptor Therapies
Let's Not Be Rash

I don’t treat any of my patients with RAS wild-type colorectal cancer with first-line cetuximab- or panitumumab-containing regimens. I don’t think you should either. Here’s why. The skin rash from use of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies is miserable, and the cost per dose is roughly double that of bevacizumab. Furthermore, anti-EGFR agents can be used in therapies other than first line to provide survival benefit to patients with RAS wild-type cancer, so their unpleasant adverse effects can be delayed until other, less noxious treatment options have been exhausted.

Even if the data convincingly showed a modest survival benefit for first-line use of anti-EGFR agents, which they do not, these toxicity and cost factors would need to be considered. The matters of how much toxicity and patient discomfort, as well as how much money, is worth how much or how little survival benefit are too often not addressed. For example, in the CALGB/SWOG 80405 trial comparing first-line use of cetuximab with bevacizumab, investigators were first given the choice of using either irinotecan hydrochloride (irinotecan/flourouracil/leucovorin calcium [FOLFIRI]) or oxaliplatin (oxaliplatin/flourouracil/leucovorin [FOLFOX]) as the chemotherapy backbone because multiple trials have shown these to be equally acceptable in terms of efficacy and overall toxicity. Both drugs are now off patent; however, during the time of study accrual, generic irinotecan was available for approximately $300 a dose, while oxaliplatin was still “on patent” and cost approximately $3000 per dose, and yet US investigators chose oxaliplatin nearly 3 times as often as irinotecan. I do not believe that we can continue to disregard substantial cost differences in the absence of compelling value for that cost.

Cost considerations aside for the moment, the data do not suggest to me that patients with RAS wild-type colorectal cancer live longer with first-line anti-EGFR treatment. Let us review the most relevant studies, CALGB/SWOG 80405 and FIRE-3.2 The 80405 trial, presented in abstract form only thus far, included 1140 patients, all with KRAS exon 2 wild-type colorectal cancer. Physicians selected either FOLFOX or FOLFIRI, and then patients were randomized to that chemotherapy plus either bevacizumab or cetuximab. The median overall survival (OS), the prespecified primary end point, was essentially the same (29.9 vs 29.0 months; hazard ratio [HR], 0.93 [95% CI, 0.78-1.09]; P = .34), as was the median progression-free survival (PFS) (10.4 vs 10.8 months; HR, 1.04 [95% CI, 0.91-1.17]; P = .55). A preliminary analysis of the patients with cancers of exclusively RAS wild type, excluding patients with any KRAS or NRAS mutation, showed essentially the same results (median OS, 32.0 vs 31.2 months; median PFS, 11.4 vs 11.3 months).3

The study reported a quality-of-life assessment and a skin satisfaction survey. Skin satisfaction was substantially lower (P < .001) in the group receiving cetuximab, and global quality of life was nonsignificantly inferior (P = .055). This result does not influence me a lot, because given the clinical experiences that we have all seen with anti-EGFR antibodies, would anyone realistically believe that the toxic effect on the skin is not an issue? The skin rash from use of anti-EGFR agents is, in my judgment, among the most unpleasant adverse effects that I ask my patients to tolerate. For an oncologist, that is saying something. We like to believe that we can effectively treat the rash, but we really cannot. Sure, we give prophylactic antibiotics and have our patients live in a sea of moisturizers and sunscreen, but at best this takes the edge off the worst of the rashes; it does not adequately ameliorate the problem. Furthermore, recall that only those patients with substantial skin rashes benefit from anti-EGFR agents, and in fact, the groups with little or no rash consistently have worse outcomes in trials than the control arm.4,5 so the patient who will benefit from an anti-EGFR therapy without experiencing a substantial skin rash is rare.

In the German FIRE-3 study,2 592 patients with KRAS wild-type colorectal cancer were treated with first-line FOLFIRI plus either cetuximab or bevacizumab. The prespecified primary end point of this trial was overall response rate in the intent-to-treat population, an unusual choice for a phase 3 trial, and one that I would have expected to favor the cetuximab group. Nevertheless, this was a trial with negative results, with primary overall response rates of 62% and 58%, respectively (P = .18). When a study is negative for its prespecified primary end point, we must consider other results to be hypothesis generating. Furthermore, and as noted by the study authors, secondary end points should be regarded as exploratory, but let us explore some of those results. The median PFS was virtually identical in both groups (10.0 vs 10.3 months; P = .55). In OS, however, the group that received up-front cetuximab had a 4.7-month survival benefit (HR, 0.77; P = .02), which became an even more impressive 8.1 months (HR, 0.70; P = .006) when the all-RAS wild-type subset was evaluated.

Why, then, am I not persuaded by the FIRE-3 data? First, the PFS was essentially identical in the 2 study groups, which must give us pause. We have been telling regulatory authorities for some time now that PFS
is a meaningful surrogate for OS. I do not think that we can have it both ways. However, the bigger problem is that, by a median of 10 months, the first-line treatment is completed and the survival curves are still right on top of each other. They do not separate until around the 2-year mark. What is happening during that more than 1-year period from progression on first-line therapy until the survival curves separate? That is not clear, but one thing that is not happening is use of second-line anti-EGFR agents in the patients who got first-line bevacizumab. Of the 295 patients in this group, all of whom had KRAS wild-type tumors, only 79 (27%) ever received either cetuximab or panitumumab. That is problematic. Recall that in the NCIC C-017 study\(^1\) the survival advantage after progression on all cytotoxic therapy of single-agent cetuximab over best supportive care in patients with exon 2 KRAS wild-type cancers was 4.7 months (median OS, 9.2 vs 4.5 months; \(P < .001\)), and we could reasonably anticipate that this would likely be higher in the all-RAS wild-type subset. We cannot know, but we can reasonably conjecture, that lack of use of EGFR agents in the non–first-line setting in those patients receiving first-line bevacizumab could account for much if not all of the survival difference between the curves.

In summary, the largest and most compelling direct comparison, CALGB/SWOG 80405, shows no benefit to the use of cetuximab over bevacizumab when given with standard first-line chemotherapy for colorectal cancer in either OS or PFS. The much smaller FIRE-3 study, a trial with negative results for its prespecified primary end point, shows no difference in PFS but shows a late separation of survival curves long after first-line therapy has been completed, and only 27% of patients in the group receiving first-line bevacizumab received anti-EGFR therapy in the second- or third-line settings, a concerning finding in a study performed only in patients with KRAS wild-type tumors. (A similar problem exists with the even smaller, much smaller, randomized phase 2 PEAK trial).\(^6\) The skin rash from anti-EGFR therapy is often a socially debilitating rash, frequently causing physical discomfort as well, and it is unreasonable to believe that such a rash does not compromise a patient’s quality of life. Furthermore, the cost per dose of the anti-EGFR agents is approximately double that of bevacizumab, yielding an added cost of several thousand dollars for each month that each patient is treated.

So I don’t use anti-EGFR agents up front. If you do, may I ask why?


\(^2\) Venook AP, Niedzwiecki D, Lenz H-J, et al. CALGB/SWOG 80405: phase III trial of irinotecan/S-FU/leucovorin (FOLFIRI) or oxaliplatin/S-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). J Clin Oncol. 2014;32(suppl 5): abstract LBA3, ASCO annual meeting.

\(^3\) Lenz H-J, Niedzwiecki D, Innocenti F, et al. CALGB/SWOG 80405: PHASE III trial of irinotecan/S-FU/leucovorin (FOLFIRI) or oxaliplatin/S-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with expanded RAS analyses untreated metastatic adenocarcinoma of the colon or rectum (mCRC). Ann Oncol. 2014;25(suppl 5): abstract S010, Proc European Society for Medical Oncology.

