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Value in Colorectal Cancer Treatment: Where it is Lacking, and Why

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Abstract

Treatment options have improved for patients with colorectal cancer, but these improvements have invariably been more modest than had been anticipated or hoped for. Yet while outcomes have improved modestly, costs have risen substantially, as prices of the newer anticancer agents in colorectal cancer have led the way in the stratospheric rise in cancer drug prices in general. Development of future strategies that will be both sustainable and attainable by all who need them will require both an understanding of past events that have brought us to the present, and a willingness to confront the limitations of our present options and to assess them for the true value that they do or do not offer.

Introduction

As patients, their families, doctors, insurers, and policy makers have slowly become aware of the staggering cost of anticancer therapy and the meteoric rise in those costs, attention has begun to focus on those circumstances in which there is a profound disconnect between the cost of care and the value of the care that that cost is delivering.¹ Nowhere is this dichotomy between cost and value more apparent than in gastrointestinal oncology in general, and in colorectal cancer (CRC) care in particular. Understanding how we got here and where we are now will be critical to establishing a future strategy that will be sustainable and deliverable to all of those who need it. Failure to confront the unsustainability of current practices, prices, and pricing trends now will invariably lead to even greater disparities in health care delivery than exist already, and such a course must not be allowed to be regarded as a viable option.

In the Beginning

For much of the second half of the twentieth century, as medical oncology began to emerge as a field, gastrointestinal (GI) malignancies remained stubbornly resistant to then-available therapeutic interventions, and GI malignancies came to be universally regarded as “chemo-refractory.” 5-Fluorouracil (5FU), an antimetabolite patented in August of 1957, was virtually the only agent available that demonstrated any meaningful antitumor activity, and

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its activity was accurately regarded as modest at best. In retrospect, the activity of 5FU was likely somewhat underestimated, in that diagnoses of GI malignancies were often made late, when patients already had large-volume disease and poor performance statuses, and so had a far less likely chance of either tolerating treatment or benefiting from it. Indeed, it remains unclear how much of the apparent progress seen in improved survival over the past several decades can be attributed to new drugs, versus how much is due to better use of surgery for metastatic disease, and better imaging leading to earlier awareness of the presence of metastatic cancer, thus creating a longer period of cancer diagnosis (lead time bias), but not necessarily as substantial a survival gain from the actual biologic onset of disease until death as has often been attributed to new drugs.²

Following the introduction of 5FU, GI oncology spent nearly the next forty years virtually wandering in a desert in terms of new drug development. It was not until 1996 that irinotecan became the second drug approved by the US FDA for use in CRC, and the brief “golden age” of CRC drug development began. Over the seven-year period from 1996 through 2003, data became available showing activity for irinotecan, oxaliplatin, capecitabine, bevacizumab, and cetuximab. Since that time, however, drug development in CRC has essentially stagnated, with only panitumumab, a drug nearly identical to cetuximab and so offering no real new clinical benefit, two additional inhibitors of the VEGF pathway, aflibercept and ramucirumab, each of which also confers no discernible benefit to patients over the already available alternative, and two oral agents, regorafenib and TAS-102, which each confer less than a two-month survival benefit, and that in highly selected group of chemotherapy-refractory patients.

Progress, However Small, at Any Price

Goldstein and El-Rayes have proposed a taxonomy of low-value care into two categories; type 1 low-value care (LVC) is defined as a new therapy that has a statistically significant but clinically modest benefit at a high cost, while type 2 LVC is a treatment that adds no additional benefit in terms of efficacy or toxicity compared with the current standard care options and has a higher cost.³ As noted above, both types of LVC have entered into CRC management.⁴ How has this occurred? Because GI oncology from the 1960’s through the early-mid 1990s was so bereft of legitimate progress, any and all activity of a novel antitumor agent was going to be gratefully embraced, as digestive tract cancers became the first of the solid tumor fields in which progress had been negligible, to show some glimmers of encouragement. As a cancer community, we were so happy to have something, anything, which “worked,” by whatever definition we chose to use at the time, that we embraced each new agent with great enthusiasm, focusing on its benefits and diverting our attention from the reality that each drug that has followed 5FU was initially designed to exceed and replace 5FU, and each has been unable to do so. The fallback position of drug development has been to then either combine that drug with 5FU in a combination regimen, or to sequence it in as a salvage therapy after 5FU failure. In that heady seven year period during which a new agent appeared on the scene seemingly every year and a half or so, there was a sense that the log jam had finally broken, and that although progress may have been slight, that this was just the beginning of what was to be an inexorable upward march towards highly efficacious and easily-tolerated treatments. Surely none of us thought that we had plateaued, or that the

plateau we had reached was high enough. Yet, after nearly four decades of virtually no progress at all, a flurry of activity was perceived and received as both hopeful and exciting.

As new drugs entered the market, however, prices began to rise, and to rise in a manner dissociated from the amount of benefit delivered, as if these increases reflected more what the preclinical hopes for the drug had been, rather than what had actually be achieved in the clinic.⁵ Helping to drive the separation of price and value was the omnipresent notion that all that we do in medicine ought to be, and therefore is, above consideration of cost. As a society we have failed to recognize for some time that this notion is both impractical and unsustainable, and each time we try to confront this we fail to effectively do so. In that context, let's look at where we are in terms of treatments for CRC, what we are paying for it, and what we are getting for our money. Currently 5FU, irinotecan, and oxaliplatin are off patent, and so relatively inexpensive generics are available, making these agents relatively minor contributors to drug costs. Whether this will remain the case or not remains to be seen. We have seen numerous situations in which an inexpensive generic drug, by accident or design, becomes limited in availability with only one supplier. Such circumstances have resulted in astronomical price increases, and current laws do not offer a remedy to this problem.⁶

Even so, recent practice, at least in the United States, indicates that oncologists have either ignored substantial price differences, or possibly have been induced by current reimbursement practices to favor the more expensive agents. An analysis of the C80405 NCI cooperative group trial in which the physicians were permitted to first make a choice between FOLFOX and FOLFIRI before patients were then randomized to receive either bevacizumab or cetuximab shows that physicians chose the oxaliplatin containing regimen approximately four times more often than the irinotecan-containing one, even though oxaliplatin at that time was still on patent and cost approximately ten times what generic irinotecan cost at the time.^{7,8} In addition, the primary results of the study showed essentially no clinical difference in outcome between use of cetuximab or bevacizumab in first line treatment of KRAS wild type CRC, and so no clinical preference was stated. This top line finding of the study was presented at the plenary session of the ASCO annual meeting in June of 2014. Segregated off in the health services outcomes presentations of the same meeting the following year, however, was an analysis showing that the cost of cetuximab was more than double that of bevacizumab.⁹ This should not lead us to the conclusion that either cetuximab or bevacizumab is an equally acceptable alternative, rather that bevacizumab, despite its already high cost,¹⁰ is the clear favorite on the basis of lower-cost, barring a particular extenuating circumstances in terms of relative risk of toxicity profile. In short, it is not that no one should get cetuximab up front, but rather that no one should unless there is a particular reason why they should not receive bevacizumab instead.

Unfortunately, the current "buy and bill" method of drug reimbursement, in which the percentage that the purchasing doctor or hospital is paid is tied to the cost of the drug, creates the undesirable but also undeniable incentive for the purchasing individual or organization to use the most expensive regimen possible. While each of us would like to believe that we were above such temptations, it would be difficult to ignore the likelihood

that an individual, perceiving no real medical difference to his or her patient, would not then be inclined to choose that course of action which is felt to be most beneficial to the provider.

Falling into the VEGF Trap

Perhaps in no place has the disconnect between value and benefit been more apparent than in the introduction of newer anti-VEGF agents into the treatment of CRC. Aflibercept, an elegantly engineered molecule designed to bind all isoforms of VEGF, was hoped to be a superior agent to the already available bevacizumab, an anti-VEGF monoclonal antibody. That this was unlikely to be the case became apparent early on in the clinical development of this agent, however, leading the developers to assiduously avoid any head-to-head comparisons with bevacizumab. They chose instead to study aflibercept in combination with FOLFIRI in second line CRC, where it showed a median improvement in overall survival of 1.4 months when added to FOLFIRI over FOLFIRI alone.¹¹ At the same time, however, a study evaluating continuation of bevacizumab beyond progression had been initiated by the AIO German cooperative group. The manufacturer of bevacizumab acquired that study in progress and substantially increased it in size. The results strikingly paralleled those of the aflibercept study, with again a 1.4 month median survival benefit for use of bevacizumab with second line therapy after its use in first line therapy as well.¹² It is noteworthy that had the trial remained with the AIO at the originally intended size, it is a very real possibility that the difference in survival would not have achieved statistical significance. It is further noteworthy that a cost effectiveness analysis of bevacizumab in both first and second line treatment of CRC found it to fail to meet any typically accepted standards of cost effectiveness.¹³ Nevertheless, when aflibercept gained FDA approval, it was placed on the market at a cost that was more than double that of bevacizumab. Comments in the media from executives involved in the marketing decisions for aflibercept noted that their price was targeted towards the 10 mg/kg dose of bevacizumab, a dose which is not listed in NCCN guidelines for any phase of CRC treatment, and which was rejected by the NCI Colon Cancer Task Force as inappropriate for study in CRC in the adjuvant setting. That the developers of aflibercept were able to locate some practitioners who were using the 10 mg/kg dose is concerning, as in the opinion of this author the use of 10 mg/kg of bevacizumab in CRC is not appropriate, and reflects either a lack of understanding of the literature at best, or cynical avariciousness at worst.

At Memorial Sloan Kettering Cancer Center in New York, upon being made aware of these cost issues, the doctors who treat CRC at that institution agreed that they did not need aflibercept to provide optimal care to their patients and so did not plan to use it. The drug was therefore not added to the hospital formulary. This decision, representing the first time to our knowledge that a new anticancer agent for a common malignancy was deliberately not added to the formulary of a major cancer center on the basis of cost, was published as an opinion piece in the mainstream media.¹⁴ Within a month of that publication, the manufacturer offered a 50% discount in the cost of the drug to all oncologists in the United States,¹⁵ showing the inherent liquidity in prices and the ability of market forces, when allowed to be brought into play, to impact on those prices.

Unfortunately, we who do not learn from history are condemned to repeat it. In 2015, the FDA approved the use of the VEGF receptor inhibitor ramucirumab in conjunction with FOLFIRI in second line treatment of CRC. The study design looked remarkably like that for aflibercept, and the results looked remarkably the same, with an extremely modest improvement in overall survival comparable to that achievable with either aflibercept or bevacizumab.¹⁶ By this time, however, ramucirumab was already on the market at more than two and a half times the price of 5 mg/kg dose of bevacizumab for use in other indications in which bevacizumab was not registered.³ Again the 10 mg/kg bevacizumab dose appears to have been the benchmark for pricing. As seen in table 1, this agent provides no meaningful benefit over the other two anti-VEGF agents. Furthermore, no data exist and no good hypothesis exists to suggest that use of one of these agents after failure of another will be beneficial. Use of ramucirumab in patients with CRC at this time is therefore inappropriate, given that at current prices it is more than twice the cost of bevacizumab, with no indication that it offers either a therapeutic advantage or an improved toxicity profile.

Small Molecules with Small Benefits and Large Price Tags

In the last several years two oral agents, regorafenib and TAS-102, have received FDA approval for use in patients with chemotherapy-refractory CRC. Each of these agents was developed in a highly selected population of patients who still had excellent performance status and good bone marrow, liver, and kidney function after progression through all available standard therapies. Even in these selected individuals, the incremental survival benefits of these agents were 1.4 and 1.8 months respectively with toxicity that was far from trivial.^{17,18} These agents entered the market in the general range of \$10,000 to \$12,000 per patient per month, the going rate for new anticancer agents at the time, regardless of the incremental degree of benefit they offered.¹⁹ These costs, well exceeding \$100,000 per patient per year, are striking both in that they offer only minimal benefit, with incremental cost effectiveness ratios that do not meet standards for cost effectiveness,²⁰ but bring home to patients the issue of direct financial toxicity, in that they are specialty pharmacy drugs which can carry patient co-pays as high as 20%.

Immunotherapy and the big step forward for a very small number

The journal Science designated immunotherapy for cancer as the most important scientific advance of the year 2013. Drugs working on a mechanism of immune checkpoint inhibition have substantially changed the landscape for therapy of melanoma, and have made meaningful progress in the care of patients with cancers of the kidney, lung, and those with lymphomas, amongst others. Progress in CRC, however, has been disappointing. The CTLA4 inhibitor tremelimumab was studied in CRC a decade ago, however the results were disappointing.²¹ Studies with PD1 inhibitors were also disappointing, with the exception of the rare subgroup of metastatic CRC patients who have both metastatic disease and tumors characterized by mismatch repair protein deficiency. To date, one prominent report has shown an encouraging response rate with some degree of durable disease control in patients with mismatch repair deficient CRC, while finding essentially no activity in mismatch repair proficient, or microsatellite stable, CRC.²² Owing to the fact that these are favorable prognosis tumors, while approximately 15% of CRCs are mismatch repair deficient, the vast

majority of these never go on to develop metastatic disease, but rather present in stages 1, 2, or 3. Only a few percent (estimates of 1%–4%) of patients who develop metastatic CRC have mismatch repair deficiency disease. For these people the PD1 inhibitor pembrolizumab has been shown to have activity. However the FDA-approved dose of this drug is 2 mg/kg every 3 weeks. The study that reported the efficacy of this drug in mismatch repair deficiency CRC, however, utilized five times that dose, or 10 mg/kg. No studies have demonstrated that a dose higher than 2 mg/kg every 3 weeks has greater efficacy. It is notable that at current prices a dose of 10 mg/kg would, for a 75 kg individual, exceed an annual price tag of \$1 million per patient per year.

This is where we are. Where will we go next?

Ultimately our problem in establishing value in CRC, as well as just about any other cancer, stems from a deep discomfort with confronting the question of just what is a given amount of benefit worth? What are we willing to pay, financially, for an extension of life by a month, or a year? Is a drug that extends life by a year worth twelve times that of one which extends life by a month? If so, is the one that extends life by a month only worth one twelfth the price of one which extends life by a year? As uncomfortable as these questions are, we must confront them or we will make no progress in getting out of the financial quagmire that we are in. At present, although we choose not to notice, we are routinely accepting a price of *at least* \$300,000 per year of life saved. This is the cost, for example of a year of life saved by adding bevacizumab or aflibercept to second line FOLFIRI. Yet if we were to use second line ramucirumab, that cost would more than double, and yet we permit such an option to be available. Clearly we have failed as a society to confront these inconsistencies between high cost and low benefit. It is a luxury we never really could afford. It is becoming clearer and clearer that we cannot afford it now. How will we deal with this? Will we muster the collective nerve and sense of responsibility to walk away from an overpriced minimal benefit, because we simply cannot and should not afford it? If the answer is no, then we are forever constrained to have more and more small benefits at higher and higher cost. Only through abandoning the practice of consistently using low value care (and paying high prices for it) will we be able to move towards high-value care for our patients. If we refused to pay a high price for low value care, then market forces will bring that price down. Until we do so, the field of CRC care will continue to be the veritable poster children for high dollar, minimal benefit, and therefore low value, care.

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Table 1

Comparison of Anti VEGF Agents in Second Line Treatment of Colorectal Cancer

A. Efficacy

Drug Name (Generic)	OS Chemo + Placebo	OS Chemo + Anti VEGF	Survival Benefit	Percent Increase in OS	Hazard Ratio
Bevacizumab ¹²	9.8 m	11.2 m	1.4 m (43 days)	14%	0.83
Ziv-aflibercept ¹¹	12.1 m	13.5 m	1.4 m (43 days)	12%	0.82
Ramucirumab ¹⁶	11.7 m	13.3 m	1.6 m (49 days)	14%	0.84

B. Price

Drug name (Generic)	Drug name (Brand)	Price Information Source	Price/mg	Price of 100 mg vial	Standard treatment dose	Price of a single 2-week dose (75 kg patient)
Bevacizumab	Avastin	Oct 2015 ASP	\$6.96	\$696.03	5 mg/kg	\$2784
Ziv-Aflibercept	Zaltrap	Oct 2015 ASP	\$8.32	\$831.50	4 mg/kg	\$2495
Ramucirumab	Cyramza	Oct 2015 NOC	\$10.79	\$1,079.42	8 mg/kg	\$6477