Biologic Agents in the Treatment of Colorectal Cancer: The Last Decade; the Lost Decade?

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The start of the new millennium brought with it the promise of solving the human genome and the capacity to design new drugs and antibodies. As a result, it also brought with it the expectations that the progress in treating disease, cancer included, would be rapid and substantial. Indeed, by the year 2000 several new “biologic” or “targeted” agents promised to be effective in cancer treatment. Imatinib turned an untreatable sarcoma, gastrointestinal stromal tumor (GIST), into one that could be managed in many patients with twice daily oral medication. And, although not as dramatic in their effect, antibodies against the EGFR and VEGF pathways had cleared the regulatory hurdles and were becoming available by early 2004 for the routine treatment of metastatic colorectal cancer.

The U.S. cooperative groups were poised to take advantage of the wealth of new biologic agents and less novel but different chemotherapeutics; the challenge was how bold to be and what magnitude of improvement to expect. As two of the cooperative groups worked on proposals with different combinations and designs, the hope for efficiency ultimately led to the single joint effort that became the Intergroup advanced colorectal cancer study: CALGB/SWOG #80405.

As designed, this three-armed study built first on a chemotherapy backbone of the treating physician’s choice: FOLFOX or FOLFIRI since data then, as now, suggested that these two regimens represented the best of our combinations of the cytotoxic agents developed in the previous decades, that they were of similar efficacy, and had toxicity profiles which were of similar intensity but different character. The study then tested the value of adding bevacizumab alone, cetuximab alone, or both antibodies to the chemotherapy. A paraffin bloc was required for EGFR staining, although patients would be enrolled without the knowledge of the result. A total of 2,289 patients would be accrued to power the study to demonstrate a Hazard Ratio of 1.25 in favor of the dual biologics (27.5 vs. 22 months) with expected accrual taking 30 months.

The study closed to accrual in March 2012, 96 months after it had opened. The final accrual was as about as planned, although just 1,177 patients with KRAS wild type tumors would be analyzed in the two-arm study comparing chemotherapy with either bevacizumab or cetuximab. The hazard ratio remained the same for a 2-sided test.

Now, nearly 10 years, seven “Dear Doctor” letters, and numerous amendments later, we await the results of that study. But rather than having expectations for major clinical advances, we have turned our hopes to the correlative science component, enabled by the mandated collection of biospecimens. It is this aspect of the trial that now holds out the most hope for a paradigm change. The primary hypothesis of the study, that dual antibody therapy would represent a safe and more efficacious therapy for patients with metastatic colorectal cancer, has already all but been refuted.

Could we have known that the questions would change, the assumptions would be wrong, and that it would take us ten years to find out? Looking back, what mistakes can we now identify that we, as a cancer community, made? More importantly, what can we learn from a critical and constructive look at our mistakes, our thought processes, our efforts, and our results that might inform our current and future projects and accelerate progress in the fight to develop better treatments for patients with colorectal cancer?

CYTOTOXICS AND THE TWENTIETH CENTURY

5-fluorouracil (5FU) was patented in August of 1957 and had the field to itself for almost four decades. The fact that no other drug demonstrated meaningful activity in colorectal cancer during that time, no doubt, accounts for the therapeutic nihilism and the perception that colorectal cancer, like all GI malignancies, was a “chemo-refractory” disease. This misconception was reinforced by the limitations of screening and surveillance techniques with the result that many patients treated in the latter third of the twentieth century had advanced bulky disease and a marginal performance status by the time that chemotherapy was first considered or initiated. Treatment with first line therapy was regarded as being of debatable benefit; second line therapy was essentially nonexistent.

This changed with the work initially reported by Shimada and colleagues,1 in which an investigational agent from the Yakult Honsha company, the 11th compound in an
exploratory series of water-soluble derivatives of the natural plant product camptothecin (designated “CPT-11”), showed activity in patients with 5FU-refractory colorectal cancer. Studies repeated in the United States confirmed efficacy, leading to accelerated approval by the U.S. Food and Drug Administration (FDA) in June of 1996. Confirmatory studies subsequently showed that this agent conferred a small but statistically significant survival benefit.

The “golden age” of colorectal cancer drug development had begun. From 1996 to 2003, oxaliplatin, capcitabine, cetuximab, and bevacizumab also became available, creating the sense that the dam had been breached, and that a veritable flood of new and more effective agents would flow from the now unfettered pipelines of pharmaceutical and biotechnology companies, and that major, dramatic progress would soon follow in the treatment of colorectal cancer. A closer look at the data, however, sheds some light on why, perhaps, those expectations were greater than they should have been.

**GREAT EXPECTATIONS**

Every drug that has entered development since 5FU has been initially designed to replace it. In that respect, every drug, including those we use today, has been a failure, and a failure that we frankly have failed to adequately acknowledge. No drug thus far has shown greater single agent activity than 5FU, and the fallback position of drug development has essential been the “if you can’t beat ‘em, join ‘em” approach: add that failed drug to 5FU, thereby creating a combination, and show that the combination is better than single agent 5FU alone. It is worth looking at the relatively modest amounts of improvement that set us on this path of combination therapy. The addition of irinotecan to 5FU added 2.2 and 3.3 months survival in the two first line randomized trials, each of which did not plan for a cross-over to sequential second-line irinotecan in the control arm. Although the results were statistically significant, there was little public debate as to whether or not they were “clinically significant” or “substantial,” and that discussion was trumped with the “proof of principle” argument: that any drug that showed activity by a new mechanism was “proving the principle” of a valid approach to the problem. With that came the tacit assumption that refinements and advances would soon follow that would bring the level of activity offered by that principle to a higher and higher level. As we have seen, however, this assumption has often not been supported by follow-up data, and, in fact, the first data have all too often been found to be the best.

**THE LAST STUDY OF CYTOTOXICS**

The last U.S. Cooperative Group colorectal trial of the twentieth century, and of the cytotoxic era, was the pivotal N9741 trial. Initially a four-arm study looking at three different schedules of irinotecan plus 5FU with a Mayo Clinic 5FU/leucovorin control arm, this trial underwent multiple closures, additions, subtractions, and refinements before its final iteration as a three-arm trial with weekly bolus irinotecan/fluorouracil/leucovorin (IFL) as the control arm, and infusional 5FU/leucovorin plus oxaliplatin (FOLFOX) and irinotecan/oxaliplatin (IROX) as the investigational arms. This study established that FOLFOX was the superior of these three final regimens. Thus, as we stood poised to enter the era of biologic therapy, the FOLFOX regimen was established as our preferred cytotoxic front-line treatment. To their credit, the French investigators who developed FOLFOX continued to tweak the regimen, using less oxaliplatin and less chemotherapy to achieve the same result with less toxicity, but no new cytotoxic agents have been developed in colorectal cancer.

**ENTER THE BIOLOGICS**

Bevacizumab, like all early “targeted” or “biologic” therapies, was envisioned to be a step beyond current cancer chemotherapy, and to replace it as a stand-alone treatment. Drugs that caused nausea, vomiting, neutropenia, diarrhea, and alopecia would go the way of bloodletting, leaches, and mercury. However, it was apparent early on that the expected single agent activity of bevacizumab was lacking, and that development strategy reverted to combination therapy. The talking points remained, however, as a lack of cytotoxic side effects of bevacizumab in colorectal cancer (a relatively non-vascular tumor) became the mantra, ignoring that it was now being joined to the same cytotoxic regimens we used to use.

Bevacizumab debuted at the 2003 ASCO Annual Meeting, when the AVF2107 study was presented by Hurwitz and colleagues. In this trial, bevacizumab when added to the IFL regimen, conferred a 4.4 month PFS advantage and a 4.7 month overall survival benefit, both highly statistically significant. At the same session in Chicago, Cunningham and colleagues presented the “BOND” trial (so-called because it was Merck KgA trial #007), confirming earlier smaller U.S. trials that showed a 23% response rate when cetuximab was added to irinotecan after irinotecan failure, and an 11% response rate when used alone after irinotecan failure. And so the

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**KEY POINTS**

- After almost 40 years of minimal progress, the period from 1996 to 2003 saw a flurry of new drugs become available.
- Progress since 2003 has been minimal.
- Most new agents with activity in the metastatic setting (irinotecan, bevacizumab, cetuximab) do not have activity in the adjuvant setting and so have not increased the cure rate.
- Combinations of biologics have been disappointing.
- Progress to date is less than we would have expected.
- Therapy individualized according to molecular characterization of each tumor appears to be the way forward.
stage was set for the decade we are now completing, from ASCO 2003 to ASCO 2013. What have we learned in this decade, what have we accomplished, and where are we headed from here?

THE LOST DECADE?

It is hard to admit, but the progress that seemed so promising in the “golden age” discussed above has been unfulfilled since 2003. (Technically, both cetuximab and bevacizumab received regulatory approval in early 2004, but the data were first presented in 2003.) First, no new mechanisms of action have been brought to bear on colorectal cancer since then; panitumumab and ziv-aflibercept appear to be variations on the existing theme, and it is debatable whether they offer any meaningful therapeutic advantage over existing agents. Regorafenib, also most likely working predominantly through VEGF but perhaps through other mechanisms as well, offers a modest survival benefit but is hardly at the level of advancement we would have predicted in 2003 that we would reach by now. In fact, what many of our trials have shown us is that many of our assumptions were wrong.

First, we assumed that adding bevacizumab to any chemotherapy backbone would represent an advance. By the time the IFL/bev data became available, the N9741 trial had shown us that FOLFOX was a superior regimen to IFL. Having no desire to resurrect IFL, which, as a result of the use of bolus 5FU and weekly irinotecan has greater toxicity than FOLFOX, regulatory authorities wisely approved bevacizumab for use in conjunction with a “5FU-containing regimen.” This, of course, translated into a de facto approval of FOLFOX plus bevacizumab which, without first-line efficacy data, became the most widely used front-line regimen in the United States as well as the basis of two large adjuvant trials (both of which failed).10,11

At the ASCO 2003 Annual Meeting, discussions were initiated that led to formally studying this regimen. The then recently activated N016966 trial, an industry-sponsored trial comparing FOLFOX to CapeOx, was redesigned as a 2x2 trial of CapeOx vs. FOLFOX with the appending of a second randomization between bevacizumab and placebo. The results were disappointing. First, CapeOx was found to be no worse, but also no better than, FOLFOX, in terms of both efficacy and safety.12,13 In terms of bevacizumab, this would technically be considered a positive trial, in that the progression-free survival was improved with a p value less than 0.05. However, the actual improvement of 1.4 months (8 months vs. 9.4 months) in progression-free survival paled in comparison to the 4.4 month improvement seen in the IFL trial, whereas the overall survival improvement (also 1.4 months) fell just short of statistical significance at p = 0.078, but far short of the 4.7 month survival benefit seen with IFL.14 Because investigators often incorrectly discontinued patients from bevacizumab when they stopped oxaliplatin for neurotoxicity, the full effect of bevacizumab may have been blunted, but even modeling for this does not project an outcome that approached that seen with IFL. Thus, the hope that adding bevacizumab to FOLFOX would bring us to the much-anticipated benchmark of a median PFS of over one year was not achieved, and that lofty goal still remains elusive.

The next assumption was that moving an agent active in the late-line setting into first line would greatly increase the activity of that agent. Cetuximab showed activity after failure of other available chemotherapies, and it was hoped that combining it with front-line therapy would lead to greater efficacy. The first indication that this was not likely to be the case was the truncated C80203 trial, which was interrupted by the availability of bevacizumab, and which failed to show a dramatic benefit in the cetuximab-containing arm.15 The first full trial to evaluate the addition of cetuximab to front-line FOLFIRI, the 1,200+ patient CRYSTAL trial, showed a statistically significant median PFS advantage, albeit of only 0.8 months, or about 24 days.16

Somewhere in this process but years later than we should have, we focused our attention on KRAS. Khambata-Ford and colleagues published evidence that exon-2 mutations in the KRAS gene conferred refractoriness to cetuximab,16 and Amado and colleagues showed the same in an even more striking manner in a large prospectively accrued trial of patients treated with panitumumab.17 In the hype about targeted therapy, we had forgotten to ask whether or not the tumor had the target. A reanalysis of the CRYSTAL data showed that patients with KRAS wild-type tumors achieved a 3-month survival benefit with front-line cetuximab, whereas those with KRAS-mutated tumors not only had no benefit but trended toward an inferior outcome.18 The first vestiges of “personalized medicine” had entered the world of colorectal cancer. Although this was a good finding, it was not the advance we had hoped for several reasons. First, evidence did not suggest that early or first-line use of cetuximab was better than last line use; a similar, perhaps even better survival benefit was shown in the KRAS wild-type subgroup that was treated with cetuximab in the salvage setting in the NCIC C017 trial.19 More importantly, KRAS was an exclusionary marker, a marker that told us who not to treat. What we all really want from personalized medicine, an inclusionary marker that tells us who to treat with an agent that otherwise would not be anticipated to work in this disease, is still lacking to this day.

The next assumption was that an empiric combination of biologic agents would be beneficial. In the so-called BOND-2 trial, a small NCI-sponsored pilot trial to assess the safety of dual antibody therapy, cetuximab plus bevacizumab, was given alone or in conjunction with irinotecan in patients with irinotecan-refractory colorectal cancer who were naïve to both antibodies. The toxicities were as would have been expected from the individual agents, and the efficacy was encouraging compared with historic controls.20 Excitement was building for the assumed improvements that bringing this dual antibody combination into front-line therapy might bring, and from this, the intergroup C80405 trial (described in the introduction) was born. It is an interesting comment on the progression of scientific thinking that nowhere in the
original 120-page correlative science protocol for C80405 is KRAS mentioned.

Two other trials occurred in parallel, however, that addressed the hypothesis that dual anti-EGFR and VEGF inhibition would result in a superior outcome. One was the so-called CAIRO-2 study. The CAIRO-2 trial essentially ignored the findings of the CAIRO-1 trial (as have most of us, because it is an inconvenient finding) and used capcitabine/oxaliplatin/bevacizumab as a control arm and added cetuximab to this regimen in the experimental arm. Not only was there no benefit to this dual antibody maneuver, but the cetuximab-containing arm had inferior progression-free survival, no benefit in overall survival, and increased toxicity. Those patients with KRAS-mutated tumors who received cetuximab did statistically significantly worse than those who did not, whereas the KRAS wild type tumors simply showed no benefit.

A similar finding was reported in the PACCE trial, which was doing a very similar study using panitumumab. Again, the addition of the anti EGFR inhibitor, in this case panitumumab, to bevacizumab plus chemotherapy (in this case, FOLFOX) not only failed to result in improved outcome, but actually led to inferior progression-free and overall survival.

The dual antibody arm of the C80405 protocol has been closed by the data safety monitoring board, and with CAIRO-2 and PACCE trials being negative, we know that dual antibody therapy with first line chemotherapy is a failed concept. Although C80405 will illuminate the relative benefits of anti EGFR compared with anti VEGF strategies in the front line setting, the greatest potential for pivotal information lies in the enormous tissue and serum bank that has been established with this trial. We have reason for optimism that this large data set will permit useful scientific inquiry that will inform our understanding of the biology of the genotypic subsets that make up the phenotype that is colorectal cancer.

In summary, following a flurry of positive studies leading to small but hopeful steps forward, the past 10 years have been a sobering period of consolidation of our knowledge and a humbling reminder that our victories have been fragile and modest, at best, and that we do not know what we think we know. The CAIRO-1 and FOCUS studies call into question the benefits of combination therapy. The N016966 trial showed us that the contribution of bevacizumab may be smaller than we cared to think, and that the interaction of this biologic with oxaliplatin-based therapy may offer less benefit than was seen with irinotecan-based treatments. The CAIRO-2 and PACCE trials show us that front line dual anti-EGFR, anti VEGF antibodies are not beneficial, and in fact, may be harmful. In addition, the COIN and NORDIC trials fail to show benefit of the addition of cetuximab to front line oxaliplatin-based chemotherapy.

Meanwhile in the adjuvant setting, we have discovered that neither irinotecan, bevacizumab, nor cetuximab contribute to the cure rate in stage III colon cancer, whereas adding oxaliplatin to concurrent radiation fails to increase the complete response rate or the cure rate in rectal cancer. Thus, how these agents, active in the macro-metastatic setting, kill tumors in the micro metastatic (adjuvant setting) is different in ways we do not currently understand.

The way forward is undoubtedly through better scientific understanding of the biology of the disease, and through individualization of therapy based on that biology. A trial looking for a treatment for all, or even most, of the patients with colorectal cancer is unlikely to show us large advances. Only through targeting specific genotypes with specific therapies might we hope to accomplish that progress. As we start the next decade in colorectal cancer treatment investigations, we must learn from our past mistakes, or we are destined to repeat them.


