Colorectal cancer represents a significant problem in Canada, with an expected 23,300 new diagnoses in 2012. Advances in surgical techniques and adjuvant chemotherapy have improved cure rates in early-stage disease, but approximately 40% of all patients will be diagnosed with or develop advanced colorectal cancer (ACRC) at some point in their disease trajectory. The past two decades of research have produced one of the most diverse systemic armamentariums of any tumour site, including cytotoxic chemotherapies, monoclonal antibodies against angiogenic targets, monoclonal antibodies against the epidermal growth factor receptor (EGFR) and most recently, tyrosine kinase inhibitors (TKI). With these advances (and with the increased use of surgical metastectomy), the median survival of patients with ACRC has doubled (Figure 1) and 5-year survivals have increased to 10%. As will be highlighted below, these survival improvements have come in small, yet steady increments and have transformed our attitude toward the treatment of ACRC from nihilistic resignation to genuine optimism.

CYTOTOXIC THERAPY

Introduced into clinical practice in the 1950s, 5-fluorouracil (5FU) remained the only treatment option for patients with ACRC for over 40 years. 5FU is a fluoropyrimidine, which exerts anticancer effects through inhibition of thymidylate synthase and subsequent impaired DNA synthesis. Since no randomized study of 5FU compared with supportive care has ever been completed, information regarding the absolute benefit of 5FU in ACRC is lacking. Our best approximation comes from a small study of 40 patients who were randomized to cisplatin plus 5FU/leucovorin (LV) versus best supportive care (BSC). The median survival in this study was 11 months compared with 5 months (p=0.006), in favour of chemotherapy, while others have suggested that the absolute survival benefit of 5FU chemotherapy is on the order of 2–3 months. Although improvements in response rates (RR) and progression-free survival (PFS) were achieved through modifications in 5FU administration and combinations with LV, estimates of overall survival (OS) remained relatively stagnant.

The late '90s brought the first meaningful improvements in the management of ACRC, with the publication of two second-line trials of the topoisomerase I inhibitor, irinotecan. Rougier et al. compared irinotecan to continuous infusion 5FU in 5FU refractory patients and demonstrated a 2.3 month improvement in survival (10.8 vs 8.5 months; p=0.035) in favour of irinotecan. Similarly, Cunningham et al. compared second-line supportive care plus irinotecan with supportive care alone. A 2.7-month median survival improvement was shown (9.2 vs 6.5 months; p<0.0001), again in favour of irinotecan. In the treatment-naive setting, a North American trial investigated the combination of irinotecan plus bolus 5FU/LV (IFL) as compared with bolus 5FU/LV and showed an improvement in OS by 2.2 months (14.8 vs 12.6 months; p=0.04). At the same time, a European study of irinotecan plus infusional 5FU/LV (de Gramont or AIO regimen) compared with infusional 5FU/LV also reported a 3.3-month OS advantage for the combination arm (17.4 vs 14.1 months; p = 0.031). In an attempt to define the optimal first-line irinotecan regimen, the BICC-C trial compared 5FU infusion plus irinotecan (FOLFIRI) to IFL and capcitabine plus irinotecan (CapeIri). 5FU infusion plus irinotecan (FOLFIRI) was associated with improved progression-free survival (PFS) as compared with IFL (7.6 vs 5.9 months; p=0.004) and...
trended toward improved OS (23.1 vs 17.6 months; \( p=0.09 \)). In addition, FOLFIRI was associated with the most favourable toxicity profile of the three regimens, thereby establishing it as a reference standard for treatment-naïve patients with ACRC.

During this period of advancement, another active agent was undergoing investigation. Oxaliplatin is a platinum-based cytotoxic agent which causes cross-linked DNA adducts and inhibition of DNA replication.\(^{14} \) In an initial Phase III study, oxaliplatin plus infusional 5FU (FOLFOX) was compared to infusional 5FU in the first-line setting. FOLFOX was associated with a longer PFS (9 vs 6.2 months; \( p=0.0003 \)), however no improvement in OS was demonstrated (16.2 vs 14.7 months, \( p=0.12 \)).\(^{15} \) A subsequent U.S. Intergroup study (N9741) randomized patients to FOLFOX, IFL or irinotecan plus oxaliplatin (IROX) and confirmed the superiority of FOLFOX for RR, PFS and OS.\(^{16} \) The 4.5-month survival advantage over IFL (19.5 v 15 months, HR 0.66; \( p=0.0001 \)) resulted in FOLFOX being considered a standard option for treatment-naïve ACRC patients. Further attempts to define the optimal first-line cytotoxic regimen have shown similar RR and OS for FOLFIRI and FOLFOX.\(^{17,18} \)

Also during this time of irinotecan and oxaliplatin investigation, the oral fluoropyrimidine, capecitabine, was added to the expanding arsenal of cytotoxic chemotherapies for ACRC.\(^{19,20} \) Although capecitabine did not show a survival advantage over bolus 5FU, its convenient oral administration was a first in the management of ACRC.

**TARGETED AGENTS**

**Bevacizumab**

Bevacizumab is a humanized monoclonal antibody against the vascular endothelial growth factor (VEGF) and is thought to exert its anticancer effect through inhibition of blood vessel normalization of vasculature and a reduction in intratumoural hydrostatic pressure.\(^{21} \) In 2004, Hurwitz et al reported the first-Phase III trial of bevacizumab, which randomised patients to IFL plus bevacizumab or placebo.\(^{22} \) The addition of bevacizumab was associated with improved RR, PFS and a 4.7-month survival advantage (20.3 vs 15.6 months, HR 0.66; \( p<0.001 \)). A similar effect was seen in a combined analysis of 3 randomized studies (2 Phase II studies and a discontinued third arm of the above-Phase III study) involving infusional 5FU plus bevacizumab in which a 3.3-month survival advantage was seen with bevacizumab.\(^{23} \) As IFL was shown to be inferior to FOLFOX,\(^{26} \) a confirmatory study of first-line bevacizumab combined with oxaliplatin-based chemotherapy was initiated (N016966). In this study, 1401 patients were randomized to FOLFOX/XELOX with or without bevacizumab. Although this study did meet its primary endpoint of improved PFS, the non-significant 1.4-month OS benefit was less than desired (21.3 months vs 19.9 months, HR 0.89, \( p=0.077 \)).\(^{24} \) In the second-line setting, FOLFOX plus bevacizumab was associated with a 2-month survival advantage over FOLFOX alone (12.9 vs 10.9 months, HR 0.75; \( p=0.0011 \)) in patients who had progressed on irinotecan-based first-line therapy.\(^{25} \) Further, a systematic review by Welch et al suggested a significant improvement in OS with the addition of bevacizumab to fluoropyrimidine-based chemotherapy in the first- or second-line settings (HR 0.79; \( p=0.0005 \)).\(^{26} \)

**EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS**

EGFR is a tyrosine kinase transmembrane receptor that is stimulated by ligands such as amphiregulin, epiregulin and transforming growth factor \( \alpha \), which leads to signaling of the Ras-Raf-MAP, PI3K and Akt pathways.\(^{27} \) These pathways are important for the regulation of cell proliferation and inhibition of apoptosis, and can be activated in colorectal cancers (CRC).\(^{28} \) The EGFR inhibitors (EGFRIs) act by preventing ligand binding and subsequent downstream signaling of oncogenic pathways. These antibodies represent a major advance in the treatment of ACRC due to their tolerability and the associated identification of a predictive biomarker. In an initial Phase II study of the chimeric monoclonal antibody cetuximab, monotherapy was compared with cetuximab plus irinotecan in irinotecan-refractory ACRC. RR and time to progression were improved with the combination, but OS was not statistically different.\(^{29} \) The first reported Phase III study of EGFRi compared panitumumab (fully humanized monoclonal antibody) plus best supportive care (BSC) to BSC alone in patients whose disease progressed despite 5FU, irinotecan and oxaliplatin. Median PFS was minimally improved (8 vs 7.3 weeks, HR 0.54; \( p<0.0001 \)) while there was no difference in OS.\(^{30} \) It is important to note that crossover was integrated in this study, and 76% of patients in the BSC arm received panitumumab. Emerging data suggested that mutations in KRAS (Kirsten rat sarcoma-2 virus oncogene) could result in a constitutively active protein and predict non-response to EGFRIs. Analysis of available specimens revealed that approximately 40% of patients had a mutation of KRAS that predicted lack of response to panitumumab, while those with wild-type KRAS (WT KRAS) had significantly longer PFS (12.3 vs 7.3 weeks) with panitumumab.\(^{31} \) At the same time, a Phase III trial (NCIC CO.17) randomized patients who had previously received (or had contraindication to) 5FU, irinotecan and oxaliplatin to cetuximab plus BSC or BSC alone. Initial results showed improvements in RR, PFS and a 1.5-month (6.1 vs 4.6 month, HR 0.77, \( P=0.005 \)) survival advantage vs cetuximab.\(^{32} \) Shortly thereafter, the predictive significance of the KRAS gene was examined, and those patients with WT KRAS tumours experienced a 4.7-month OS improvement (9.5 vs 4.8 months, HR 0.55, \( p<0.001 \)), while those with mutations of KRAS derived no benefit from the antibody.\(^{33} \)

EGFRIs have been examined in earlier settings of ACRC with contradictory results. The original publication of the CRYSTAL study showed that the addition of cetuximab to FOLFIRI resulted in improved PFS, while an updated analysis revealed a 3.5-month survival advantage over FOLFIRI (23.5 vs 20 months, HR 0.796, \( p=0.0093 \)) for WT KRAS patients. A trend toward improved OS (23.9 vs 19.7, \( p=0.07 \)) was also suggested for WT KRAS patients in the PRIME study of FOLFOX with or without panitumumab.\(^{36} \) Conversely, the MRC COIN trial did not show any benefit from adding cetuximab to FOLFOX even in the WT KRAS population,
Disease control rates (68% vs 54%) and PFS (5.7 vs 4.1 months) were superior, while the median OS was improved by 1.4 months (11.2 vs 9.8 months, HR 0.81; p=0.0062) in favour of bevacizumab. No new safety concerns were identified with continuation of bevacizumab and an exploratory analysis revealed that the treatment effect was not dependent on KRAS mutation status. In this selected population, the median OS from the start of first-line therapy was not dependent on KRAS mutation status. In this study, benefits were also seen in those patients who had received prior bevacizumab. Adverse events (Grade 3/4) were more common in the aflibercept arm (83.5% vs 62.5%) and included those typical of anti-VEGF therapy (hypertension, hemorrhage, arterial/venous thromboembolic events and proteinuria), as well as increased chemotherapy-associated toxicities (diarrhea, asthenia, stomatitis, infections, palmar-plantar erythrodysesthesia, neutropenia and thrombocytopenia).

**REGORAFENIB**

Regorafenib is an oral multikinase inhibitor of several protein kinases, including VEGFR1-3, TIE2, KIT, RET, RAF1, BRAF, PDGFR and FGFR which are involved in angiogenesis, oncogenesis and the microenvironment. Due to promising disease control rates in a Phase Ib study in ACRC, a Phase III trial (CORRECT) randomized patients (ECOG 0-1) whose disease had progressed (or had toxicity) on fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, cetuximab or panitumumab (WT KRAS), to regorafenib or placebo. The primary endpoint was OS and patients were randomized 2:1 to regorafenib 160 mg daily or matched placebo for 3 weeks of a 4-week cycle. Disease control rates (41% vs 15%) and PFS were significantly better for regorafenib (6.4 vs 5.0 months, HR 0.77, p=0.0052). Grade 3 or 4 adverse events were more common with regorafenib (54% vs 14%) with the most common being hand-foot skin reaction, fatigue, diarrhea, hypertension, and rash/desquamation. There was no difference in deterioration of quality of life and health status from baseline to end of treatment in both arms of the study. This study also gave us some modern-day survival information in patients who are well enough to receive third/fourth line therapy, as the median time from diagnosis of metastases to randomization in this trial was 31 and 29.9 months for regorafenib and placebo patients, respectively.

**CONCLUSION**

Over the past 15 years, significant advancements in the management of ACRC have occurred and resulted in a doubling of median survivals. These gains can be attributed to advances in surgical oncology, as well as the plethora of cytotoxic and targeted agents now available for ACRC. As history has shown us, systemic therapy achievements have come in small incremental gains ranging from 1.4 to 4.7 months (Table 1), and importantly, they have not been at the cost of quality of life. The pharmacoeconomics of ACRC therapies have always

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**Table 1. Trials reporting significant improvements in overall survival by line of therapy.**

<table>
<thead>
<tr>
<th>Study</th>
<th>1st line (months)</th>
<th>2nd line (months)</th>
<th>3rd line (months)</th>
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<tbody>
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<tr>
<td>Rougier et al</td>
<td>10.8 vs 8.5</td>
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<tr>
<td>Cunningham et al</td>
<td>9.6 vs 6.5</td>
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<td>Saltz et al</td>
<td>14.8 vs 12.6</td>
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<td>17.4 vs 14.1</td>
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<tr>
<td>Karapetis et al</td>
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<td>Van Cutsem et al</td>
<td>23.5 vs 20*</td>
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<td>Grothey et al</td>
<td>6.4 vs 5.0</td>
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* WT KRAS; 5hd/4hd line

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**RECENT ADVANCES**

**Bevacizumab beyond progression**

Based on preclinical and observational data, it has been hypothesized that improvements in disease may be achieved with ongoing VEGF inhibition with bevacizumab after disease progression. To test this hypothesis, a European study (ML18147) randomized patients who had previously progressed on first-line bevacizumab (with irinotecan or oxaliplatin-based chemotherapy) to bevacizumab plus chemotherapy or chemotherapy alone. Similarly, a smaller Phase III Italian study has recently reported improved PFS with continuation of bevacizumab beyond progression.

**AFLIBERCEPT**

Aflibercept is a recombinant fusion protein of the extracellular domains of VEGF receptor 1 (VEGFR1) and VEGFR2 fused with the constant region of human immunoglobulin G1. This protein binds VEGFA, VEGFB and placental growth factor, which are thought to be important regulators of angiogenesis and progression. Since preliminary studies suggested tolerability and disease stabilization in ACRC, a large Phase III trial (VELOUR) was undertaken to explore the effect of aflibercept (or placebo) added to FOLFIRI in the second-line setting after progression on oxaliplatin-based chemotherapy. In addition to improved RR and PFS, aflibercept was associated with an improvement in median survival by 1.44 months (13.5 vs 12.0 months, HR 0.817, p=0.0032). In a prespecified analysis, benefits were also seen in those patients who had received prior bevacizumab. Adverse events (Grade 3/4) were more common in the aflibercept arm (83.5% vs 62.5%) and included those typical of anti-VEGF therapy (hypertension, hemorrhage, arterial/venous thromboembolic events and proteinuria), as well as increased chemotherapy-associated toxicities (diarrhea, asthenia, stomatitis, infections, palmar-plantar erythrodysesthesia, neutropenia and thrombocytopenia).
been a matter of debate; hopefully future molecular studies will identify predictive biomarkers and subgroups of patients most likely to benefit.

Population-level studies will be important in determining whether or not the most recent benefits seen in clinical trials are additive and translate into meaningful survival improvements for ACRC as a whole. With the recent genomic profiling of colorectal cancers by the Cancer Genome Atlas project and ongoing efforts to molecularly subtype colorectal cancers, we have good grounds to be optimistic about further progress.

References