Updates in adjuvant systemic therapy for colon cancer

Research focuses on identifying patients who will most benefit and on minimizing long-term side effects

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Abstract
Colon cancer is common in Canada and leads to significant morbidity, mortality, and social and economic impact. In 2010, the estimated incidence of colorectal cancer in Canada was 22,500 cases, with 9100 deaths. In early-stage colon cancer, surgery remains the primary curative procedure. However, due to increased risk of recurrence, adjuvant treatment is now a well-established standard of care. Adjuvant treatment has become more complex with the addition of new chemotherapy regimens that have proven active against this disease. As well, molecular prognostic and predictive tools have emerged to better tailor therapy to higher-risk populations. This overview summarizes changes in adjuvant treatment of colon cancer over the past decade, including: modification of the TNM classification system; the role of adjuvant systemic treatment in Stages II and III colon cancer; issues surrounding treatment in the elderly; and optimal timing of chemotherapy following surgery. Adjuvant systemic treatment of colon cancer continues to be an area of active research, with a focus on identifying patients who will benefit most from chemotherapy and minimizing the long-term side effects.

Keywords
Colon cancer, adjuvant systemic treatment, overview

Epidemiology
Colon cancer is the second most common malignant disease in developed countries, with 1 million new cases and 500,000 deaths worldwide. In Canada, the estimated incidence of colorectal cancer (CRC) for 2010 is 22,500, with 9100 deaths. It is the second highest cause of cancer deaths after lung cancer. CRC patients, their families and friends experience enormous social, emotional and economic effects.

This review will discuss new changes in the TNM classification system, the role of adjuvant systemic treatment in Stages II and III colon cancer, and issues surrounding adjuvant treatment in the elderly and optimal timing of chemotherapy following surgery.

Changes in TNM staging for CRC
The American Joint Committee on Cancer (AJCC) has recently published a revised staging manual reflecting updated overall survival (OS) statistics. Table 1 shows the major changes in 5-year survival according to the Surveillance, Epidemiology and End Results (SEER) observations. The importance of satellite tumour deposits is now defined by the new site-specific factor category “Tumor Deposits (TD)” that describes their texture and number. Lesions that lack regional lymph node metastasis but have tumour deposit(s) will be additionally classified as N1c. The number of lymph nodes positive for metastasis influences prognosis in both N1 and N2 groups. In addition, metastatic disease parameters have been expanded, with M1a for single, vs M1b for multiple, metastatic sites. It is important to be aware of these changes, as they affect treatment decisions and results of clinical trials initiated after 2010 that defined disease using the new staging system.

Chemotherapy for stage III colon cancer
While patients with Stage III colon cancer are curable, they are at high risk of recurrence (>60%). Adjuvant chemotherapy following surgical resection has been established since 1990, when Moertel showed that fluoruracil (FU or 5FU) and levamisole yielded a reduced relative recurrence rate of 41% (p<0.0001) and improved OS of 33% (p≈0.006). Eight years later, O’Connell reported that 6 months of treatment resulted in the same benefit as 12 months. FU has since been

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<td><strong>Old TNM AJCC 6th edition</strong></td>
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the backbone of adjuvant treatment, with leucovorin (LV) replacing levamisole, which all randomized trials use as their control arm. In order to improve the tolerance of this treatment, capcitabine, an oral prodrug of FU, was shown to be noninferior to FU with improved relapse-free survival (hazard ratio [HR]=0.86; 95% confidence interval [CI]=0.74–0.99; p=0.04) and fewer adverse events (p<0.001). Two major Phase III clinical trials with a combined 4,653 randomized patients showed a 20% relative risk reduction of disease-free survival (DFS) and an absolute OS benefit of 4.3% when adding oxaliplatin to FU-based chemotherapy. An added toxicity from oxaliplatin has been peripheral neuropathy and increased neutropenia. Based on these trials, the standard chemotherapy for Stage III colon cancer is now FOLFOX (FU, LV, oxaliplatin).

CHEMOTHERAPY FOR STAGE II COLON CANCER

The benefits of adjuvant FU-based chemotherapy have been clearly demonstrated in Stage III colon cancer. However, in Stage II disease, chemotherapy’s added benefit is controversial. Even in the 2007 QUASAR (QUick And Simple And Reliable) trial, which demonstrated a survival advantage of adjuvant FU-based chemotherapy among Stage II patients, the benefit for the average patient was modest (5-year OS, 80.3% vs 77.4%; p=0.04). Clinical and pathologic features have been used to identify Stage II patients at higher risk of recurrence. American Society of Clinical Oncology (ASCO) guidelines suggest discussing adjuvant chemotherapy with medically fit patients who have any of the following high-risk features: inadequately sampled lymph nodes (<12); T4 lesions; tumour perforation; and/or poorly differentiated histology.

A variety of molecular prognostic and predictive factors are being developed to assist in identifying high-risk Stage II patients, including microsatellite instability (MSI), also known as DNA mismatch repair deficiency (dMMR) and genotyping. Approximately 15% of CRCs are characterized by high levels of MSI (MSI-H), a marker of dMMR. Colorectal tumours with dMMR are unable to correct mismatches during DNA replication, resulting in cumulative DNA mutations. Testing can be done either by immunohistochemistry for the most commonly lost MMR proteins (MLH1, MSH2, MSH6 and PMS2) or by the polymerase chain reaction (PCR) assay. MSI-H tumours are characterized by their predominantly right-sided proximal location in the colon, poorer differentiation, mucinous histology and peritumoural lymphocytic infiltration.

Patients with Stage II colon cancer and MSI-H who are treated with surgery alone have a better prognosis than microsatellite stable patients. Stage II MSI-H patients do not seem to benefit from adjuvant FU single-agent chemotherapy, in fact, data suggest it may be detrimental. In the setting of Stage II disease for individuals who have no ASCO high-risk features and MSI-H, we will often lean against adjuvant chemotherapy after thorough discussion with the patient.

Gene expression profiling, such as ColoPrint® and Oncotype DX® Colon Cancer Assay, is also emerging as a tool to improve prognostication of Stage III and, more important, Stage II colon cancer. ColoPrint®, an 18-gene prognostic classifier that identifies patients as high- vs low-risk, has recently been validated in 2 independent test sets, including Stage II patients. In multivariate analysis among patients with Stage II colon cancer, the signature had a HR of 3.315 and 4.216 and was superior to the ASCO criteria in assessing the risk of cancer recurrence. The PARSC trial (Prospective Study for the Assessment of Recurrence Risk in Stage II Colon Cancer Patients Using ColoPrint®) is currently testing ColoPrint®, and will help us better understand if it can improve the prognostication of Stage II patients.

O’Connell et al recently reported on the development of Oncotype DX® Colon Cancer Assay using gene analysis quantitative reverse transcription PCR (RT-qPCR) on RNA extracted from fixed, paraffin-embedded tumours. They identified 7 prognostic genes and 6 predictive genes (for FU/LV), and used an algorithm to assign patients to low-, intermediate- and high-risk groups. These algorithms were tested against 1,436 patients enrolled in the adjuvant Stage II QUASAR study. The recurrence score did predict for recurrence risk, DFS and OS. As well, in multivariate analysis, recurrence score was prognostically (p=0.008) independent of MMR and other clinical pathologic factors examined.

SYSTEMIC THERAPIES WITHOUT EFFICACY IN STAGE III DISEASE

Once systemic therapies have shown benefit in advanced cancer, they are tested in the adjuvant setting. Attempts to move certain systemic therapies with proven efficacy in metastatic CRC to the adjuvant setting have been surprisingly unsuccessful. For example, clinical trials evaluating the addition of irinotecan to FU/LV in resected CRC showed no benefit in DFS and OS. More recently, monoclonal antibody agents such as cetuximab, targeting the epidermal growth factor receptor (EGFR), and bevacizumab, targeting the vascular endothelial growth factor (VEGF), have failed to show improved DFS when added to adjuvant chemotherapy. A recent editorial outlined hypotheses as to why VEGF inhibition failed in the adjuvant setting. Theories generated, none of which are universally accepted, include rebound angiogenesis with discontinuation of antiangiogenesis inhibitors and VEGF inhibition-induced hypoxia (secondary to vessel pruning), which may promote malignancy. An important lesson stems from these trials, namely that colorectal tumours behave differently in the primary and metastatic settings. We cannot assume that activity in the metastatic setting translates to activity in the adjuvant setting. Appropriate trials must be conducted and research needs to focus on understanding the molecular differences between tumours of various stages.

COLON CANCER IN THE ELDERLY

The incidence of colon cancer in older patients is rising; 40% of cases are diagnosed in patients older than 75 years of age, and the median age at diagnosis is 71 years. Thus, colon cancer represents a significant health problem in this population. Although the elderly compose a large proportion of patients with colon cancer, they are under-represented in randomized controlled trials (RCTs). Data regarding their specific benefit are usually biased, as patients who are recruited to these trials are generally fit and do not have major comorbidities.

A pooled analysis of individual patient data from 7 Phase III randomized trials (n= 3,351) compared the effects of
adjuvant FU-based chemotherapy with those of surgery alone in patients with Stage II or III colon cancer. The improved OS from adjuvant treatment was similar across age groups for the first 5 years of followup. Survival curves for patients older than 70 years of age converged slightly after 5 years, probably because of deaths from other causes.24 Similar results were found among patients aged 80 years and older.26 Importantly, these two analyses did not find an increase in toxicity among older patients.

A pooled analysis from the ACCENT (Adjuvant Colon Cancer End Points) trial using data from 10,499 patients <70 years and 2170 patients >70 years of age had contradicting results.27 Patients participated in 6 Phase III adjuvant trials comparing FU to combinations with irinotecan, oxaliplatin or oral FU (capcitabine and tegafur-uracil [UFT]/LV). All outcome measures, including OS, were statistically significantly improved for those in the experimental vs standard arms in younger patients (HR=0.86; 95% CI=0.79–0.92) but not in older ones (HR=1.14; 95% CI=0.98–1.32). These results were consistent regardless of type of chemotherapy given in the experimental arm; Of note, disease-specific survival was not reported in the analysis, so the issue of cancer-unrelated deaths (which are more often observed in older individuals) was not taken into account. Given the contradicting analyses, the pros and cons of chemotherapy should be discussed with patients in this age group and chemotherapy should not be denied based on age alone.

**Optimal Timing of Adjuvant Chemotherapy**

A critical question that has never been addressed in a randomized clinical trial is the optimal timing to start adjuvant chemotherapy for colon cancer following surgical resection. A recent abstract presented at the 2011 ASCO GI Symposium28 assessed the relationship between time to adjuvant chemotherapy and survival using a systematic review and meta-analysis of 9 studies (2 RCTs and 7 registry/population-based studies), with a total of 14,357 colon and rectal cancer patients in the era of FU-based chemotherapy. The meta-analysis for OS showed a HR of 1.12 (95% CI=1.09–1.15) for every 4-week delay in adjuvant chemotherapy, the authors found an approximately 12% decrease in OS. In a smaller, registry-based study of 1,053 patients, OS rates of patients with Stage III colon cancer who received adjuvant chemotherapy prior to 12 weeks were similar; however, if chemotherapy was further delayed, an OS detriment was observed.29 These data suggest that efforts need to be implemented to ensure a timely initiation of adjuvant chemotherapy.

**References**

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**Disclosures**

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