Colorectal Oncology Research Review™

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In this issue:

Abbreviations used in this issue:

5-FU = 5-fluorouracil; **CAPOX** = capecitabine and oxaliplatin; **CI** = confidence interval; **CRC** = colorectal cancer; **DFS** = disease-free survival; **DPD** = dihydropyrimidine dehydrogenase; **EGFR** = epidermal growth factor receptor; **FOLFOX** = 5-fluorouracil, leucovorin, and oxaliplatin; **HR** = hazard ratio; **IROX** = irinotecan and oxaliplatin; **mCRC** = metastatic colorectal cancer; **MDT** = multidisciplinary team; **MSI** = microsatellite instability; **NS** = not significant; **OS** = overall survival; **PFS** = progression-free survival; **QOL** = quality of life.

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Welcome to the 27th issue of Colorectal Oncology Research Review, a unique Australian publication bringing you some of the most important research from around the world.

In this issue we review two studies that evaluated the non-inferiority of short-course oxaliplatin-containing adjuvant therapy in stage II/III CRC. The difference in efficacy between 3 and 6 months of chemotherapy was negligible in lower-risk patients, but the difference in toxicity and impact on QOL may be of more clinical significance and favoured the shorter course. We hope you find these and the other studies reviewed this issue interesting and of use in your clinical practice. We welcome your comments and feedback.

If you have colleagues or friends within Australia who would like to receive our publication, send us their contact email and we will include them for the next issue.

Kind Regards,

Dr. Matthew Burge

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Duration of adjuvant chemotherapy for stage III colon cancer

Authors: Grothey A, et al.

Summary: Non-inferiority of adjuvant therapy with either FOLFOX or CAPOX given for 3 or 6 months was evaluated in a prospective, pre-planned pooled analysis of six randomised phase 3 trials in stage III colon cancer. Non-inferiority was based on DFS at 3 years and was confirmed if the upper limit of the 95% CI of the HR did not exceed 1.12. Non-inferiority of 3 months vs 6 months of treatment could not be confirmed after 3263 events of disease recurrence or death reported in the overall population of 12,834 patients (HR 1.07; 95% CI 1.00, 1.15). However, the 3-month regimen was non-inferior to the 6-month regimen for patients treated with CAPOX (HR 0.95; 95% CI 0.85, 1.06), particularly among lower-risk patients with T1, T2, or T3 and N1 cancers.

Comment: This represents a huge, investigator-initiated, international effort, of which Australia was part. Its importance cannot be overstated. This type of study in stage III colon cancer will never be repeated and will provide a wealth of useful, practice-guiding data as time goes on. For now, it seems that any difference in efficacy between 3 and 6 months of chemotherapy is very small and not of clinical significance for many patients, particularly when the vast improvements in toxicity (most notably neuropathy) are considered. In deciding how long to continue oxaliplatin-based chemotherapy for stage III disease, lower risk patients (T3 and N1) and those treated with oxaliplatin/capecitabine seem particularly suited to a 3-month course.

Reference: N Engl J Med. 2018;378(13):1177-1188.
Abstract

3 versus 6 months of adjuvant oxaliplatin-fluoropyrimidine combination therapy for colorectal cancer (SCOT)

Authors: Iveson TJ, et al.

Summary: Oxaliplatin-containing adjuvant therapy given for 3 months was non-inferior to 6 months of the same therapy in a phase 3 study of 6088 patients with high-risk stage II and stage III CRC. Patients were randomised 1:1 to receive either 3 or 6 months of adjuvant chemotherapy with CAPOX (n=4107) or FOLFOX (n=1981). Non-inferiority was based on DFS and the non-inferiority margin was a hazard ratio of 1.13. After 1482 DFS events, 3-year DFS rates were 76.7% for the 3-month treatment group and 77.1% for the 6-month treatment group. Non-inferiority was confirmed (HR 1.006; 95% CI 0.909, 1.114). The incidence of grade ≥2 peripheral neuropathy was higher in the 6-month vs 3-month treatment group (58% vs 25%) and was long-lasting and associated with worse QOL. The authors commented that although the study was underpowered, the data are suggestive of similar survival outcomes with improved QOL with shorter oxaliplatin-containing adjuvant therapy.

Comment: The SCOT study was the largest contributor to the IDEA meta-analysis discussed above. The study was slightly underpowered due to a lower than expected number of events, but was still able to demonstrate non-inferiority of 3 months vs 6 months of adjuvant oxaliplatin-based therapy. In SCOT, a majority (approximately 2/3) of patients received CAPOX and the IDEA analysis found a statistical interaction between the choice of regimen (CAPOX or FOLFOX) and the impact of 3 months' vs 6 months' treatment on 3-year DFS. Non-inferiority was proven for CAPOX but not FOLFOX. However, caution should be exercised given the chemotherapy regimen was not randomised but chosen by the investigator. Nonetheless, these data provide a robust basis for communicating to our patients any benefit of longer duration adjuvant treatment versus the well quantified additional toxicity and QOL impacts, thus allowing for fully informed decision-making.

Reference: Lancet Oncol. 2018;19(4):562-578.
Abstract

Targeting HER2 in colorectal cancer: The landscape of amplification and short variant mutations in *ERBB2* and *ERBB3*

Authors: Ross JS, et al.

Summary: Comprehensive genomic profiles of 8887 mCRC cases (85.5% colonic, 14.5% rectal) were evaluated for genomic alterations in cancer-related genes, tumour mutational burden, and MSI. A total of 569 cases were positive for *ERBB2* (4.8%) and/or *ERBB3* (1.7%). High tumour mutational burden (≥20 mutations/Mb) was more common in *ERBB*-mutated CRCs and high MSI was more common in *ERBB3*-mutated CRCs ($p<0.002$). The frequency of *KRAS* alterations was significantly reduced in *ERBB2* amplification samples compared with all mCRC. Notably, 32% of *ERBB2*-positive CRCs had short variant alterations that are undetectable by routine immunohistochemistry or fluorescence in situ hybridization testing.

Comment: This analysis of genomic alterations in a large number of mCRC cases focuses on *ERBB2* (HER2) and *ERBB3* (HER3), revealing the frequencies and range of oncogenic abnormalities together with associated genetic alterations. HER2 amplifications were present in approximately 3–5% and were associated with wild-type *KRAS* and lower mutational burden, consistent with previous studies that amplification of HER2 is most common in left-sided *RAS* wild-type tumours and represents another resistance mechanism to EGFR antibodies. Nevertheless, approximately 15–20% of amplified cases did harbour a concurrent *KRAS* mutation and it's not known whether these cases respond as well to HER2-directed therapies. Mutations in HER2 occur more commonly among higher mutational burden tumours (including MSI high) and activate the receptor. Emerging data indicates these cases may also respond to HER2-directed tyrosine kinase inhibitors such as lapatinib. However, these mutations would not be detected by HER2 immunohistochemistry or fluorescence in situ hybridization testing.

Although small, a significant percentage of our patients harbour HER2 alterations so we will need to develop methods to routinely identify them and enable access to treatments, because HER-targeted therapy is effective.

Reference: Cancer. 2018;124(7):1358-1373.
Abstract

Phase 2 study of treatment selection based on tumor thymidylate synthase expression in previously untreated patients with metastatic colorectal cancer

Authors: Meropol NJ, et al.

Summary: Thymidylate synthase expression was found to be prognostic in a phase 2 study of 211 patients with previously untreated mCRC. Patients with low thymidylate synthase expression treated with FOLFOX plus bevacizumab had a longer median PFS than those with high thymidylate synthase expression (13 months vs 9 months; $p=0.04$) and longer median OS (32 months vs 21 months; NS). Patients with high thymidylate synthase expression were randomised to receive treatment with FOLFOX plus bevacizumab or IROX plus bevacizumab, but there were no significant differences between treatments for PFS (9 months vs 10 months) and OS (21 months vs 18 months).

Comment: Once again, a predictive biomarker study for standard chemotherapeutic agents has failed to find anything that clinicians can use in daily practice. This study mirrors many other efforts, including the recently presented MAVERICC study where *ERCC1* expression levels did not correlate with differential benefit for oxaliplatin- over irinotecan-containing regimens in first-line mCRC. To me, it seems very unlikely such predictive biomarkers will ever make their way into daily clinical practice. Of interest is the use of IROX in this study. This regimen has randomised data supporting its use and is perhaps a forgotten option for patients who cannot tolerate fluoropyrimidines, such as those with DPD deficiency and 5FU-related cardiac toxicity.

Reference: Cancer. 2018;124(4):688-697.
Abstract

Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair–deficient/microsatellite instability–high metastatic colorectal cancer

Authors: Overman MJ, et al.

Summary: Nivolumab in combination with ipilimumab provided a durable clinical benefit in patients with DNA mismatch repair–deficient /MSI-high mCRC enrolled in the CheckMate-142 study. A total of 119 patients received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg once every 3 weeks (four doses) followed by nivolumab 3 mg/kg once every 2 weeks. Investigator-assessed objective response rate was 55% after a median follow-up of 13.4 months. The study is still ongoing and median duration of response was not reached. PFS rates were 71% and OS rates were 85% at 12 months. Clinically meaningful improvements were observed in patient-reported outcomes, including functioning, symptoms, and QOL. Grade ≥3 treatment-related adverse events were manageable and occurred in 32% of patients, but 13% of patients discontinued treatment because of treatment-related adverse events.

Comment: Undoubtedly, the recent discovery that checkpoint inhibitors are active against MSI CRCs has been a major breakthrough. Responses are common and usually durable. Updated results of Keynote 164, investigating pembrolizumab in this setting, will be presented at the upcoming ASCO annual meeting. Unanswered questions include exactly when these drugs should be used, whether they are more or less active in subtypes of MSI (such as those with Lynch syndrome or *BRAF* mutations) and whether and in whom combinations are really needed. Randomised studies are ongoing. It seems certain that immunotherapy will play a major role in the future against these cancers, wherever the primary site. Furthermore, use in earlier stage disease may also be successful and studies in stage III microsatellite unstable colon cancers are underway.

Reference: J Clin Oncol. 2018;36(8):773-779.
Abstract

Prognostic value of primary tumour resection in synchronous metastatic colorectal cancer

Authors: van Rooijen KL, et al.

Summary: Primary tumour resection improved survival in asymptomatic mCRC according to analysis of individual patient data of 3423 patients enrolled in eight randomised controlled trials of systemic therapy in the ARCAD database. The analysis included patients with unresected synchronous mCRC (n=710), resected synchronous mCRC (n=1705) and metachronous mCRC (n=1008). Median OS was significantly worse in the unresected group (16.4 months) compared with the synchronous resected group (22.2 months; HR 1.6; 95% CI 1.43, 1.78) and metachronous group (22.4 months; HR 1.81; 95% CI 1.58, 2.07) after adjusting for age, gender, performance status and prior chemotherapy. Median PFS was also significantly worse in the unresected group compared with the synchronous resected group (HR 1.31; 95% CI 1.19, 1.44) and metachronous group (HR 1.47; 95% CI 1.30, 1.66). The authors commented that the reasons for (non)resection were not available and the results may be subject to bias.

Comment: Whether or not to resect the primary tumour in the setting of mCRC is a common topic of discussion at MDTs. Due to more effective combination chemotherapy regimens and low rates of complications (even when bevacizumab is used) from primary tumours during a patient's life-time, resection of primaries is often not performed. Outside a curative treatment goal, we consider it when the primary is (near) obstructing or bleeding and the volume of metastatic disease is low. Whether resection by itself leads to longer patient survival in the setting of unresectable metastases seems unlikely to me. The question can only be answered by prospective randomised trials and these are being performed. So in time we should have an answer, although it may not be straightforward. Perhaps it will depend on whether the primary is left or right sided!

Reference: Eur J Cancer. 2018;91:99-106.
Abstract

Independent commentary by Dr. Matthew Burge, a medical oncologist and staff specialist at the Royal Brisbane Hospital and a visiting specialist at the Rockhampton Base Hospital. He undertook his undergraduate training in Manchester, UK before moving to Australia in 1996. After obtaining his FRACP in 2004 he moved back to the UK to undertake a clinical fellowship in GI malignancies with professor Matt Seymour in Leeds. He moved to Brisbane in 2007 to take up his current position. His clinical and research interests are in GI malignancies, particularly colorectal cancer and neuroendocrine tumours. Dr Burge has been a local investigator for AGITG and international trials, served on trial management committees and is a member of the AGITG lower GI working party.

References: 1. Douillard JY, *et al. N Engl J Med* 2013;369(11):1023–34. **2.** Vectibix® (panitumumab) Approved Product Information. Available at: www.amgen.com.au/Vectibix.PI. **3.** Van Cutsem E, *et al. Ann Oncol* 2016;27(8):1386–1422. **4.** PBS website. Available at: www.pbs.gov.au. Accessed June 2017.

Circulating cell-free DNA as predictor of treatment failure after neoadjuvant chemo-radiotherapy before surgery in patients with locally advanced rectal cancer

Authors: Schou JV, et al.

Summary: High baseline plasma levels of cell-free tumour DNA were found to be associated with increased risk of recurrence, shorter time to recurrence, and shorter DFS in two biomarker studies of 123 patients with locally advanced rectal cancer. All patients were treated with neoadjuvant chemoradiotherapy prior to total mesorectal excision and 42% of patients received induction chemotherapy with CAPOX. After a median follow-up of 55 months, distal or local recurrence was seen in 31% of patients. Those with baseline cell-free tumour DNA above the 75th quartile had a higher risk of local or distant recurrence and shorter time to recurrence than patients with cell-free tumour DNA below the 75th quartile (HR 2.48; 95% CI 1.3, 4.8; p=0.007). DFS was also shorter in patients with baseline cell-free tumour DNA above the 75th quartile (HR 2.43; 95% CI 1.27, 4.7; p=0.015). The authors commented that cell-free DNA could potentially improve pre- and post-treatment risk assessment for patients with locally advanced rectal cancer.

Comment: Undoubtedly circulating cell-free tumour DNA is a promising biomarker. Specific mutations are searched for in plasma based on known mutations previously found in the patient's histologic tumour specimen. Researchers from the Walter and Eliza Hall Institute of Medical Research have previously demonstrated the prognostic importance of the presence of cell-free DNA and randomised studies evaluating the impact of cell-free DNA on clinical practice are underway in stage II and III colon and rectal cancers, among others. This Danish study further supports the prognostic utility in rectal cancer and suggests that not just the presence, but also the level of circulating DNA is important.

Reference: Ann Oncol. 2018 1;29(3):610-615.
Abstract

Napabucasin versus placebo in refractory advanced colorectal cancer

Authors: Jonker DJ, et al.

Summary: The efficacy of napabucasin, a first-in-class cancer stemness inhibitor that targets STAT3, was investigated in a double-blind randomised phase 3 trial in patients with refractory advanced CRC. Accrual in the trial was stopped for futility after 282 patients had undergone randomisation to oral napabucasin 480 mg every 12 h (n=138) or placebo (n=144) in addition to best supportive care. All patients had good performance status and had been treated unsuccessfully with all available standard therapies. There was no difference in OS between the napabucasin and placebo groups (4.4 months vs 4.8 months; HR 1.13; 95% CI 0.88, 1.46; p=0.34). In a subgroup of 55 patients with pSTAT3-positive tumours, OS was longer with napabucasin vs placebo (5.1 months vs 3.0 months; HR 0.41; 95% CI 0.23, 0.73; p=0.0025). Napabucasin-treated patients had a higher incidence of treatment-related diarrhoea (79% vs 19%), nausea (51% vs 24%) and anorexia (38% vs 16%) than patients who received placebo. The most common severe (grade ≥3) treatment-related adverse events included abdominal pain (4% vs 3%), diarrhoea (15% vs 1%), fatigue (10% vs 6%) and dehydration (4% vs 1%).

Comment: Many patients with mCRC are motivated and remain well enough to be considered for additional therapy after all standard treatments are exhausted. Indeed, this is an area of very high unmet need. Thus trials such as this are to be commended. It is very disappointing that the trial was stopped early for futility, nevertheless important lessons may well emerge from the data generated. It is likely that subsets of patients' tumours will have differential sensitivity to drugs such as napabucasin and teasing out the predictive biomarkers is essential. It may be that recruitment of an unselected population masks any benefit in the sensitive subset. After all, a trial of Herceptin in all comers with metastatic breast cancer may well have produced a negative result, but tossing Herceptin into the bin as a result would have been a massive mistake! In this regard, the high STAT-3 expresser sugbroup is a reasonable starting point. Let's hope the investigators and biotech (Boston Biomedical) are able to uncover the most sensitive patient subsets and target future research efforts to them.

Reference: Lancet Gastroenterol Hepatol. 2018;3(4):263-270.
Abstract

Inhibition of EGFR, HER2, and HER3 signalling in patients with colorectal cancer wild-type for *BRAF*, *PIK3CA*, *KRAS*, and NRAS (FOCUS4-D)

Authors: Adams R, et al.

Summary: This phase 2/3 study tested the hypothesis that combined inhibition of EGFR, HER2, and HER3 signalling will control growth of all wild-type tumours in CRC. Patients with newly diagnosed advanced CRC or mCRC whose tumour was wild-type for *BRAF*, *PIK3CA*, *KRAS*, and *NRAS* were randomised to receive the tyrosine kinase inhibitor AZD8931 40 mg twice daily (n=16) or placebo (n=16). Unfortunately the study was discontinued after the first pre-planned interim analysis due to lack of activity. AZD8931 had no PFS benefit with a median PFS of 2.96 months compared with 3.48 months with placebo. The most common grade 3 adverse event was skin rash which was reported in 3 patients treated with AZD8931 and no patients who received placebo.

Comment: FOCUS 4 is a new type of clinical trial design aiming to improve efficiency of drug evaluation in rationally molecularly-selected patient subsets. It has many attractions, but also many challenges and complexities. In this analysis, a novel tyrosine kinase inhibitor of the family of HER receptors was tested in a subset in which these receptors were predicted to play a major role in tumour growth because the cells did not harbour mutations in downstream *RAS*, *BRAF* or PI3-kinase pathways. Unfortunately the drug was not active, emphasizing our lack of understanding of the complex interplay between these receptors. Despite its purported importance, inhibiting HER3 has met with failure to date in CRC. A study comparing cetuximab to an EGFR/HER3 inhibitor was also negative. When targeting this family of receptors, only the antibodies inhibiting EGFR, cetuximab and panitumumab (in *RAS* wild-type tumours) have demonstrated a survival advantage, although HER2 inhibition in HER2 overexpressing tumours is also a promising strategy.

Reference: Lancet Gastroenterol Hepatol. 2018;3(3):162-171.
Abstract

Dose-response effects of aerobic exercise among colon cancer survivors

Authors: Brown JC, et al.

Summary: Higher volumes of moderate-intensity aerobic exercise were found to be feasible and safe in a randomised phase 2 trial of 39 patients who had been recently treated for stage I–III colon cancer. Patients were randomised to low-dose aerobic exercise (150 min per week; n=14), high-dose aerobic exercise (300 min per week; n=12) or usual care (control; n=13). Over 6 months, the low-dose group was 92.8% adherent completing 142 min of exercise per week and the high-dose group was 89.0% adherent completing 247 minutes of exercise per week. Favourable changes in soluble intercellular adhesion molecule-1 were evident in the low-dose group (-134.9 ng/mL) and high-dose group (-114.8 ng/mL) compared with the control group. No changes were observed for soluble vascular adhesion molecule-1. There were no serious adverse events.

Comment: Since the introduction of oxaliplatin into adjuvant chemotherapy protocols in 2004, minimal progress has been made to improve the prognosis for patients with stage III colon cancer. Various chemotherapeutic and biologic agents have failed to further improve outcomes. Non-pharmacologic strategies might be more successful. This small study investigated aerobic exercise up to 5 hours per week for 6 months. The authors found that exercise prescriptions were well adhered to and were safe. Furthermore, reductions were seen in intercellular adhesion molecules which have previously been implicated as poor prognostic markers in this setting and in enabling the growth of micrometastases. The ongoing international CHALLENGE randomised trial, in which Australia is playing a major role, is enrolling several hundred patients to standard of care versus a prescribed exercise programme, after chemotherapy. This study has already demonstrated that patients in the intervention arm are increasing their exercise by the required amount, with no unforeseen safety concerns. It is hoped this study will definitively answer the question as to the role exercise may play in improving survival for patients with stage II and III colon cancer.

Reference: Clin Colorectal Cancer. 2018;17(1):32-40.
Abstract

