ASCO Conference Review

Colorectal Oncology

Making Education Easy ASCO Annual Meeting, Chicago 2007

In this issue:

Welcome to ASCO Conference Review,

a locally focused summary of some of the most exciting clinical research on Colorectal Oncology presented at the ASCO Annual Meeting last month.

This Review has been created to allow those unable to attend, but with a keen professional interest in colorectal oncology medicine, to access a summary of significant clinical studies presented that are likely to affect current practice. Selection and review of the research is carried out independently by Associate Professor David Perez, who recently attended the ASCO Annual Meeting in the US. The Review also provides website links to key studies in the field.

I hope you find the conference review stimulating and look forward to your feedback.

Kind Regards

Dr Shaun Holt
Medical Advisor
shaunholt@researchreview.co.nz

Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): the CRYSTAL trial

Authors: Van Cutsem E et al

Summary: This trial explored the activity of cetuximab in combination with standard FOLFIRI compared with FOLFIRI alone as a first-line treatment for patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer. Of a total of 1217 patients, 608 received cetuximab at an initial dose of 400 mg/m2 followed by weekly doses of 250 mg/m2/week plus FOLFIRI every 2 weeks (Group A), while the remaining 609 patients received FOLFIRI alone (Group B). Median progression-free survival time was significantly prolonged in Group A, compared with Group B (8.9 months vs 8 months). The response rate was also significantly higher in Group A, compared with Group B (46.9% vs 38.7%). The most common grade 3/4 adverse events were neutropenia (26.7% Group A, 23.3% Group B), diarrhoea (15.2% and 10.5% respectively), and cutaneous reactions (18.7% and 0.2% respectively). The authors reported that these adverse reaction rates were as expected from known adverse effects of cetuximab. In conclusion, the addition of cetuximab to FOLFIRI reduces the relative risk of progression by approximately 15%, significantly increases response rate and significantly prolongs progression-free survival in the first-line treatment of patients with metastatic colorectal cancer.

Comment: A modest improvement in median progression-free survival at the expense of increased skin toxicity and diarrhoea. Unfortunately, quality of life benefits were not assessed. Once again, the degree of skin toxicity was predictive of the degree of progression-free survival advantage. Greater benefits may have been anticipated with EGFR-positive tumours but an IHC assay was used which is less predictive than FISH.

Reference: *Journal of Clinical Oncology,* 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 4000

About Research Review

Research Review is an independent publisher producing electronic journals to help make education easier for the NZ medical community.

Impact on quality of life of adding cetuximab to irinotecan in patients who have failed prior oxaliplatin-based therapy: the EPIC trial

Authors: Eng C et al

Summary: The multinational phase III EPIC trial explored the impact of cetuximab on survival in 1298 patients with pretreated epidermal growth factor receptor-expressing metastatic colorectal cancer, 648 of whom received cetuximab 400 mg/m2 followed by 250 mg/m2 weekly plus irinotecan 350 mg/m2 every 3 weeks and 650 received irinotecan alone. Baseline Health-Related Quality of Life (HRQoL; as assessed by the EORTC QLQ-C30 questionnaire, version 3.0) scores were significantly different between treatment arms for 4 of the 15 scales (Social Functioning, Fatigue, Dyspnoea, and Appetite Loss), in favour of the cetuximab plus irinotecan arm. Combination therapy was superior to irinotecan monotherapy in progression-free survival (hazard ratio 0.69) and response rate (16.4% vs 4.2%). The authors speculated that the between-group similarity in overall survival may have been to subsequent therapy (46% of irinotecan monotherapy recipients received cetuximab, 89% of them in combination with irinotecan). During treatment, HRQoL was better preserved and showed less deterioration in symptom scores (pain, nausea, insomnia) as well as global health scores in the combination treatment group, compared with the irinotecan monotherapy group.

Comment: An apparent improvement in quality of life with the addition of cetuximab to chemotherapy. However, the cetuximab cohort had better baseline quality of life and performance status which may have biased the results in favour of cetuximab. There was no survival advantage; however, most patients receiving chemotherapy only subsequently received cetuximab. In view of the high cost of cetuximab, a cost/utility analysis would be informative.

Reference: *Journal of Clinical Oncology,* 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 4003

Oxaliplatin/5FU/LV in adjuvant colon cancer: Updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of six years

Authors: de Gramont A et al

Summary: In the MOSAIC trial, 2246 patients with completely resected stage II (40%) or III (60%) colorectal cancer received 5-FU/LV or FOLFOX4 (5-FU/LV plus oxaliplatin) every 2 weeks for 12 cycles. The study's primary endpoint (3-year disease-free survival for the overall population) significantly favoured the FOLFOX4 regimen over 5-FU/LV alone (André et al. NEJM 2004;350:2343-51). Final disease-free survival, at 5 years' follow-up, confirmed the benefit of FOLFOX4 (hazard ratio 0.80). In addition, at a median follow-up of 6 years, FOLFOX4 showed a significant benefit in overall survival in stage III colorectal cancer (hazard ratio 0.80). According to long-term safety data, there was no increase in the rate of secondary cancer (5.0% in both treatment arms). In conclusion, the MOSAIC trial data demonstrate a significant survival advantage with the FOLFOX4 regimen in the adjuvant treatment of stage III colorectal cancer.

Comment: The 6-year MOSAIC survival data solidify the value of oxaliplatin in the adjuvant treatment of stage III colonic cancer. This was achieved at some cost with 12.4% suffering grade 3/4 neuropathy. Quality of life was not assessed in this study. It is disappointing that a survival advantage was not evident for stage II disease, particularly since a progression-free survival advantage for stage II was still seen at the 5-year point.

Reference: *Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 4007

Sequential compared to combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (ACC): A Dutch Colorectal Cancer Group (DCCG) phase III study

Authors: Punt CJ et al

Summary: In this study, Dutch investigators investigated overall survival of 820 previously untreated patients with advanced colorectal cancer, median WHO PS 0-2, who were randomised to receive first-line capecitabine (Cap), second-line irinotecan (Iri), and third-line Cap + oxaliplatin (CapOx) (Arm A, sequential) or first-line CapIri and second-line CapOx (Arm B, combination). Patients were followed-up for a median 32 months. Median overall survival in Arm A was not significantly different from that in Arm B (16.3 months vs 17.7 months). Overall grade 3/4 toxicity over all lines did not differ significantly except for grade 3 hand-foot syndrome (13% in Arm A and 6% in Arm B). Eleven deaths were considered probably related to treatment (neutropenic sepsis and/or diarrhoea, 8 in Arm A, 3 in Arm B) and involved protocol violations in some. Regarding first-line therapy, significant differences in grade 3/4 toxicity in Arm A versus Arm B included diarrhoea (10% vs 25%, respectively), febrile neutropenia (1% vs 6%, respectively) and hand-foot syndrome (12% vs 5%, respectively). The 60-day all-cause mortality was 3.0% (n=12) in Arm A and 4.5% (n=18) in Arm B. In conclusion, combination therapy offered no survival advantage over sequential therapy in patients with advanced colorectal cancer. Both treatment strategies are valid options in this patient population.

Comment: This is the first phase III study to assess sequential versus combination chemotherapy using all 3 of the major colorectal chemotherapy drugs. Although quality of life was equal in both arms, there was more gastrointestinal and haematological toxicity with combination therapy, although skin toxicity was less. The equivalence of overall survival results indicates that single-agent capecitabine is appropriate first-line chemotherapy, particularly for frailer patients.

Reference: *Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 4012

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Independent commentary by Associate Professor David Perez, Medical Oncologist, Dunedin Hospital.

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Meeting the 12 lymph nodes (LN) benchmark in colorectal cancer surgery: A comparison of NCCN and SEER data

Authors: Rajput A et al

Summary: The American College of Pathology has suggested the examination of ≥12 lymph nodes from patients treated surgically for colorectal cancer to adequately stage the disease. Both ASCO and the National Comprehensive Cancer Network (NCCN) have considered adopting the 12 lymph node protocol as a benchmark for quality cancer control. Upon comparing outcomes data from NCCN specialty centres and the Surveillance Epidemiology and End Results (SEER) programme, this study found that ≥12 lymph nodes were examined in 89% of patients with newly diagnosed stage I-III colon or rectal cancer who underwent primary surgery at NCCN centres in 2005 and 2006, compared with 45% of colorectal patients diagnosed in 2002 in a SEER region. NCCN data revealed that, compared with stage III patients, stage I patients were significantly less likely to achieve the 12 lymph node target (odds ratio 0.20) as were those with rectal cancer (odds ratio 0.44). In conclusion, whereas the majority of NCCN centres remove and examine ≥12 lymph nodes as part of an oncological resection, this target is achieved in less than half of cases in population-based samples. Further studies will determine whether increasing the number of lymph nodes examined is an important quality measure that may be linked directly to patient outcomes.

Comment: This retrospective study suggests that harvesting at least 12 lymph nodes may improve outcomes for colorectal cancer. Stage migration is definitely demonstrated but a prospective study will be required to show whether outcomes are improved. The interpretation of node count for rectal cancer is problematic and depends on whether neoadjuvant radiotherapy +/- chemotherapy has been administered.

Reference: *Journal of Clinical Oncology,* 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 4015

The impact of dietary patterns on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803

Authors: Meyerhardt JA et al

Summary: This prospective observational study assessed the influence of diet on 1009 patients with stage III colorectal cancer enrolled in a phase III adjuvant chemotherapy trial. A food frequency questionnaire investigated patients' diets during and 6 months after adjuvant chemotherapy. Two major dietary patterns were identified: a prudent pattern, associated with a higher intake of fruits, vegetables, poultry and fish; and a Western pattern, associated with a higher intake of red meat, fat, refined grains and desserts. Data for all patients were combined and analysed according to quintiles of each dietary pattern. A higher intake of a Western pattern diet after cancer diagnosis was associated with significantly worse disease-free survival; the adjusted hazard ratio was 3.15 for patients in the highest quintile of Western pattern diet intake, compared with those in the lowest quintile. Similar outcomes were seen for recurrence-free survival and overall survival, whereas no such results were associated with the prudent dietary pattern. In conclusion, a higher intake of a Western pattern diet may increase the risk of recurrence and mortality in surgically resected stage III colorectal cancer treated with adjuvant chemotherapy. "*Further studies are needed to delineate which components of such a diet are most influential".*

Comment: This study raises some interesting questions about the impact of diet on colorectal cancer prognosis. Patients in the highest quintile of the 'Western' diet appeared to have substantially worse disease-free survival and overall survival. Although the analysis adjusted for many confounders there was no account taken of total energy intake. A mechanism for this dietary effect was not offered by the investigators. Pending further evaluation, it would not be unreasonable to recommend a 'prudent' diet to patients following colorectal cancer surgery.

Reference: *Journal of Clinical Oncology,* 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 4019

How well do we communicate with patients concerning adjuvant systemic therapy? A survey of 150 colorectal cancer survivors

Authors: Love N et al

Summary: This study reports data from 150 patients treated with adjuvant chemotherapy for colorectal cancer in the last 5 years, who were interviewed as to their level of understanding regarding risks and benefits of adjuvant chemotherapy. Patients were also asked whether they would undergo the same chemotherapy again for varying absolute treatment benefits, and about their expectations of and experiences with adjuvant chemotherapy side effects. At the same time, 24 colorectal cancer clinical investigators and 150 medical oncologists were asked to predict how patients would respond. About 1/3 of patients would accept adjuvant chemotherapy again for a 1% absolute reduction in recurrence risk (ARRR), and about 2/3 believed a 5% ARRR would justify treatment; corresponding estimates of clinical investigators and medical oncologists were lower. In addition, adjuvant chemotherapy side effects differed from expectations: 57% and 66% of patients experienced less GI toxicity and alopecia, respectively, while 38% and 46% of patients receiving oxaliplatin experienced greater cold intolerance and numbness. In conclusion, many potential obstacles prevent effective communication with patients about adjuvant chemotherapy, including heterogeneity in patients' attitudes towards risk/benefit trade-offs and preconceptions about treatment side effects. The authors suggest that further research could evaluate how an audio/web education supplement affects the decision-making process.

Comment: This report is similar to findings in patients with breast cancer. However, there may be several biases. Patients who have received adjuvant chemotherapy have a vested interest in chemotherapy and this may influence their responses. In addition, a truer picture would be obtained if patients who had relapsed after adjuvant therapy were included. As noted in previous studies, oncologists generally overestimate the benefits patients expect to encounter on chemotherapy.

Reference: *Journal of Clinical Oncology,* 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 4020

EGFR, HER2 and Kras as predictive factors for cetuximab sensitivity in colorectal cancer

Authors: Finocchiaro G et al

Summary: This study aimed to identify biological predictors for sensitivity/resistance to cetuximab in colorectal cancer and compared biomarker results in primary tumours and corresponding metastases. Analyses were conducted of the epidermal growth factor receptor (EGFR) (IHC, FISH), HER2 (FISH), and KRAS (mutation) in paraffin embedded tumour blocks from 85 colorectal cancer patients treated with cetuximab. For FISH analyses, a positive result was defined according to criteria described in breast (Wolff et al. J Clin Oncol 2007;25:118-45), lung (Cappuzzo et al. JNCI 2005;97:643-55) and colorectal cancer (Moroni et al. Lancet Oncology 2005;6:279-86). In this study, biomarker assays revealed a significant benefit in response and time-to-tumour progression for EGFR FISH positive patients, compared with EGFR FISH negative patients. EGFR expression assessed by IHC was not associated with any clinical endpoint. Increased HER2 gene copy number was associated with shorter time-to-tumour progression and survival. In KRAS mutation carriers, the relative response was significantly lower, time-to-tumour progression was shorter, as was survival, compared with patients with wild-type KRAS. Primary and metastatic tumour tissue analyses revealed no difference between these sites for EGFR FISH, HER2 FISH and KRAS results.

Comment: These data suggest that EGFR measured by FISH has a much better predictive value for response to anti-EGFR therapies than does the IHC technique. In view of the high cost of these agents, a predictive test is very welcome. The predictive contributions of HER-2 and KRAS mutations may allow a combined index to enable much better targeting of anti-EGFR agents. Confirmatory studies are needed.

Reference: *Journal of Clinical Oncology,* 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 4021

^{18}F-FDG PET changes management and improves prognostic stratification in patients with colorectal cancer: results of a prospective, multi-centre study

Authors: Scott AM

Summary: This study examined the impact of PET in changing management in patients with proven or suspected recurrence of colorectal cancer and assessed the impact of management change on disease-free survival. Patients were subdivided into Group A (symptomatic with a residual structural lesion suspicious for recurrent tumour) or Group B (patients with pulmonary or hepatic metastases, which were potentially resectable as determined by conventional imaging); all underwent PET scans and followed for 12 months to determine actual management and to assess clinical outcomes. Of a total of 191 patients, PET detected additional sites of disease in 48.4% of Group A and 43.9% of Group B patients. Management plans were changed in 65.6% of Group A and 49.0% of Group B patients. Follow-up confirmed implementation of management plans in 96% of patients. Analysis of follow-up data to 12 months post-PET revealed that progressive disease was identified in 60.5% of Group A patients with additional lesions detected on PET compared with conventional imaging, and 36.2% of patients with no additional lesions were detected by PET; corresponding values for Group B were 65.9% and 39.2% of patients, respectively. PET also provided valuable prognostic information in patients stratified into curative/palliative intent groups. The authors state that their data *"unequivocally demonstrate the significant impact of PET on management and outcomes in patients with suspected recurrent colorectal cancer".*

Comment: This study demonstrates that FDG-PET identifies further metastatic lesions in approximately 50% of patients and this frequently leads to a change in management plan. The investigators suggest this may translate into improved prognosis, however, a randomised study would be required to show this definitively. It is unlikely such a study will ever be done as data such as these make so much intuitive sense.

Reference: *Journal of Clinical Oncology,* 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 4025

Phase III trial of capecitabine + oxaliplatin (XELOX) vs. 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX4) as 2nd-line treatment for patients with metastatic colorectal cancer (MCRC)

Authors: Rothenberg ML

Summary: This phase III study compared XELOX with FOLFOX4 in 627 patients previously treated with irinotecan in combination with bolus and/or infusional 5-FU/LV for metastatic colorectal cancer. The study's primary endpoint, time-to-tumour progression, was met with a progression hazard ratio of 0.97 for the XELOX group. Median time-to-tumour progression was similar between the groups (4.8 months for XELOX- and 4.7 months for FOLFOX4-treated patients), as was overall survival, with a death hazard ratio of 1.03 for the XELOX group. Median survival was 11.9 months for XELOX- and 12.6 months for FOLFOX4-treated patients. Grade 3/4 toxicities occurred in 60.1% of XELOX- and 72.4% of FOLFOX4-treated patients. Among treatment-related grade 3/4 adverse events, the most common were: diarrhoea (20% XEOLOX vs 5% FOLFOX4), neutropenia (5% vs 35%, respectively), fatigue (5% vs 8%, respectively), paresthesia (9% vs 8%, respectively), and nausea/vomiting (6% vs 5%, respectively). Grade 3 hand-foot syndrome rates were 3.5% with XELOX and 0.6% with FOLFOX4. The 60-day all-cause mortality was 3.9% in XELOX- and 4.2% in FOLFOX4-treated patients. The authors conclude that second-line treatment with XELOX is non-inferior to FOLFOX4 in terms of progression-free survival, overall survival and response rates. They add that the safety profile was similar to previous studies, with no unexpected toxicities.

Comment: It now seems conclusive that XELOX and FOLFOX are equivalent for metastatic colorectal cancer. This was designed as a non-inferiority study so no comment is possible about one regimen being superior. The toxicities differed between the regimens in a predictable way but overall there was less grade 3/4 toxicity with XELOX. In view of the logistical advantage of XELOX this appears to be the regimen of choice, with FOLFOX reserved for those who suffer excessive gastrointestinal toxicity with XELOX.

Reference: *Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 4031

Supported by an unrestricted educational grant by Roche Products (New Zealand) Limited. Roche have no control over editorial content.

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