Colorectal Oncology Research Review™

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Issue 3 - 2012

In this issue:

Welcome to the 3rd 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 discuss the genetic basis of CRC and the prognostic and treatment implications. We review several studies in metastatic CRC, including evaluation of two novel agents: TAS-102, an oral nucleoside, and aflibercept, an anti-angiogenic agent. Analysis of the CRYSTAL and ICE studies showed cetuximab provided significant survival benefits to patients with *KRAS* G13D tumours when given first line, while a small phase II study showed clinical benefit with cetuximab rechallenge. The burden of bone metastases in CRC and the survival benefits of zoledronic acid are described in a large observational study, while a small study showed no benefit of yttrium-90 radioembolisation in liver metastases.

Independent Commentary has been provided by Dr Eva Segelov, Associate Professor of Medicine, St Vincent's Clinical School and Medical Oncologist, St Vincent's Hospital, Sydney, and Dr Jeremy Shapiro, Associate Professor, Department of Medicine, Monash University and Gastro-Intestinal Medical Oncologist, Alfred and Cabrini Hospitals, Melbourne.

We hope you enjoy our selection for this edition and your comments and feedback are welcome. 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 Janette Tenne

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Infusion of calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in colorectal cancer: a systematic review and meta-analysis

Authors: Wu Z et al

Summary: This meta-analysis of seven studies, including four randomised controlled trials and a total of 1238 participants, did not support the hypothesis that infusion of calcium and magnesium (Ca/Mg) can reduce the occurrence of oxaliplatin-related sensory neurotoxicity. The OR was not significant for any grade of neurotoxicity. Conversely, the meta-analysis supported the hypothesis that infusion of Ca/Mg has no effect on the efficacy of oxaliplatin-based chemotherapy, with no significant effect on the relative risk for tumour response rate. The authors concluded that 'large-scale, randomised, controlled clinical trials will be required to confirm these hypotheses.'

Comment (ES): The use of Ca and Mg infusions pre- and post-oxaliplatin remains controversial and is variably used across Australia, despite inclusion in several guidelines such as eviQ. The infusions add considerable time to the delivery of any oxaliplatin-containing regimen, with resultant cost and manpower implications, as well as quality-of-life issues for patients who are usually on 2- or 3-weekly visits to the chemotherapy centre. The history of Ca/Mg use is tainted by the interim analysis from the CONcePT trial in mCRC for which well publicised reports of decreased efficacy of oxaliplatin were initially a cause of great concern, halting recruitment to ongoing prospective placebo-controlled studies, which were examining the neuroprotective benefit of Ca/Mg infusions. However, subsequent independent analysis of radiological response from CONcePT found that Ca/Mg did not reduce chemotherapy efficacy, in fact, the response rate favoured the Ca/Mg arm. This article presents a meta-analysis from a Chinese group who analysed seven studies comprising >1200 patients, which support the findings demonstrating no loss of oxaliplatin efficacy, but do not support reduction in either grade 2 or all grade neurotoxicity. Confusing the picture further is the failure of most publications to clearly differentiate between acute and chronic neurotoxicity. The authors suggest a large-scale, randomised trial to confirm their findings, but this is unlikely ever to be performed due to inability to attract funding. In view of this meta-analysis, the first published in this area, it remains unclear whether Ca and Mg infusions are necessary.

Reference: Eur J Cancer 2012;48(12):1791-1798

http://www.ejcancer.info/article/S0959-8049(12)00281-X/abstract

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Independent commentary by Dr Eva Segelov and Dr Jeremy Shapiro

Dr Eva Segelov is an Associate Professor of Medicine, St Vincent's Clinical School and Medical Oncologist, St Vincent's Hospital, Sydney. She is the current Chair of the Gastrointestinal Cancer Group of the Clinical Oncological Society of Australia (COSA) and has been the Convenor of the COSA Annual Scientific Meeting from 2008-2010.

Dr Segelov is also a lead researcher in the AGITG, currently the Australian Principal Investigator for the QUASAR2 study, and co-PI for the SCOT trial and the ICECREAM study of cetuximab in G13D mutant CRC. Her clinical practice centres around upper and lower GI cancers, as well as breast cancer. Dr Segelov has an ongoing interest in medical education and holds the positions of Director of Medical Student Education at St Vincent's Clinical School, and Director of Conjoint Liaison for the Faculty of Medicine, UNSW.

Dr Jeremy Shapiro is an Associate Professor in the Department of Medicine, Monash University and a Gastro-Intestinal Medical Oncologist at the Alfred and Cabrini Hospitals in Melbourne.

He is a key researcher in the AGITG, where he is the Study Co-Chair for the International Co20 trial and the ICECREAM study, both evaluating novel approaches in refractory colon cancer. Dr Shapiro leads the GI Research program at Cabrini Hospital, is the Chair of the National EVIQ Medical Oncology Committee, and is the author of over 60 peer reviewed publications/abstracts.

To PET or not to PET? That is the question. Staging in anal cancer

Authors: Bhuva NJ et al

Summary: PET/CT was found to alter staging in 42% of cases in a retrospective review of 43 patients treated radically for anal cancer at Mount Vernon Cancer Centre in the UK between 2009 and 2010. All patients were scanned using conventional modalities (DRE, MRI and CT) and using PET/CT. Although the PET/CT stage differed from MRI, it did not lead to changes in management. PET/CT showed greater sensitivity for detection of lymph nodes and the study demonstrated a distinct trend towards upstaging of anal cancer with PET/CT.

Comment (ES): Mount Vernon is a leading academic centre in the area of anal cancer, with significant contributions to management through difficult-to-conduct randomised controlled trials, aimed at maximising treatment response and thereby cure. This article describes a review of methods of disease staging, comparing conventional modalities (DRE, MRI and CT) with PET/CT scans. The benefit for PET/CT has previously been documented particularly for defining node metastases, which are present in 30% of patients at diagnosis but are difficult to assess. This study found that PET/CT altered staging in 42% of patients overall, with 5% demonstrating previously undetected distant metastatic disease. Nodal staging altered in 32%, both upstaging and downstaging, consistent with the benefit of PET in nodal staging of other pelvic tumours such as cervix and vulval cancers. This may translate to a more targeted radiotherapy treatment volume, especially with the use of IMRT, thereby reducing late toxicity, which is of vital importance in this highly curable malignancy. Although not funded in Australia, PET/CT as a one-off, upfront investigation in this curable cancer seems very reasonable, with as robust data as one can ever obtain in a rare tumour to demonstrate efficacy.

Reference: Ann Oncol 2012;23(8):2078-2082
http://annonc.oxfordjournals.org/content/23/8/2078.abstract

Abbreviations in this issue:

AGITG = Australasian Gastro-Intestinal Trials Group; **CEA** = carcinoembryonic antigen; **CRC** = colorectal cancer; **CT** = computed tomography; **DFS** = disease-free survival; **DRE** = digital-rectal examination; **EGFR** = endothelial growth factor receptor; **HR** = hazard ratio; **IMRT** = intensity-modulated radiation therapy; **MRI** = magnetic resonance imaging; **OR** = odds ratio; **OS** = overall survival; **PET** = positron emission tomography; **PFS** = progression-free survival; **SIRT** = selective internal radiation therapy; **VEGF** = vascular endothelial growth factor

Prognostic gene expression signature associated with two molecularly distinct subtypes of colorectal cancer

Authors: Oh SC et al

Summary: This paper reported the identification of a gene signature in CRC that independently predicted response to chemotherapy and clinical outcome. The gene signature was associated with OS and DFS in 177 patients with CRC and validated in two independent cohorts of 213 patients. The signature was an independent risk factor for overall survival with a HR of 3.08 (95% CI 1.33 to 7.14; p=0.008). It was also able to identify a subset of patients with stage III cancer who had a significantly better outcome with adjuvant chemotherapy.

Comment (ES): The race to find a clinically useful (i.e. predictive) gene signature for CRC, particularly in the adjuvant setting, is progressing with multiple groups all over the world. They are using various techniques to identify a molecular signature that will guide therapy, as well as inform prognosis. There is pressure to commercialise such a test and a number of these have entered the market, with direct marketing overseas to patients, who likely will be starting to ask their oncologists about such tests. This publication from MD Anderson describes a gene expression signature of 114 genes derived from genome-wide screening that appears to discriminate between two types of CRC and predict the benefit of adjuvant chemotherapy, especially in patients with stage III disease. DNA was extracted from primary tumours of patients with stage III CRC who had received either adjuvant fluoropyrimidine alone or in combination with oxaliplatin. There was some overlap of the genes with those forming the basis of other signatures such as Oncotype DX colon. Due to small numbers, the paper was unable to demonstrate more than a positive association of their gene signature with outcome. Independent validation of these signatures is necessary before they become useful on a day-to-day basis.

Reference: Gut 2012;61:1291-1298
http://gut.bmj.com/content/61/9/1291.abstract

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Association of *KRAS* G13D tumor mutations with outcome in patients with metastatic colorectal cancer treated with first-line chemotherapy with or without cetuximab

Authors: Tejpar S et al

Summary: The association between *KRAS* mutation status and treatment outcomes was investigated in 1378 patients with metastatic CRC treated with first-line chemotherapy with or without cetuximab. All patients participated in the CRYSTAL and OPUS studies and 533 had *KRAS* mutant tumours: G13D (16%), G12V (23%), other mutations (61%). The addition of cetuximab to first-line chemotherapy seemed to benefit patients with *KRAS* G13D tumours in terms of tumour response (40.5% vs 22.0%; OR 3.38; p=0.042) and progression-free survival (median 7.4 vs 6.0 months; HR 0.47; p=0.039). There was no significant effect for overall survival (median 15.4 vs 14.7 months; HR 0.89; p=0.68). Patients with G12V and other mutations did not benefit from the addition of cetuximab to first-line chemotherapy. Patients with G13D mutation had a significantly worse response to chemotherapy alone than patients with other mutations (22.0% vs 43.2%; OR 0.40; p=0.032).

Comment (ES): Given the Australia-wide opening of the investigator-initiated, AGITG-supported ICECREAM trial, this paper is further confirmation that the subgroup of metastatic CRC patients who carry the specific *KRAS* exon 2 G13D mutation may benefit from EGFR inhibition. Originally presented at ASCO 2011, this paper documents the response in G13D tumours in the two first-line cetuximab plus chemotherapy trials, showing benefit for the addition of the biological agent. It is therefore important to document which type of *KRAS* mutation is present in your patients. Please allow this unashamed plug for the ICECREAM trial and refer any patients with a G13D mutation to a centre participating in the trial (ICECREAM@ctc.usyd.edu.au). This is the only way to access cetuximab, which is not otherwise available for *KRAS* G13D patients despite this encouraging new data.

Reference: J Clin Oncol 2012;30(29):3570-3577
http://jco.ascopubs.org/content/30/29/3570.long

TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial

Authors: Yoshino T et al

Summary: The efficacy and safety of TAS-102, a novel oral nucleoside antitumour agent, was investigated in this phase II double-blind, placebo-controlled study in 169 patients with metastatic CRC. All patients had received ≥2 regimens of standard chemotherapy and were refractory or intolerant to fluoropyrimidine, irinotecan and oxaliplatin. Patients were randomised to receive placebo or oral TAS-102 35 mg/m^2 twice daily for 5 days followed by a 2-day rest period and then a 14-day rest period to comprise a 28-day cycle. After a median follow-up of 11.3 months, TAS-102-treated patients had a median OS of 9.0 months (95% CI 7.3 to 11.3) compared with 6.6 months (95% CI 4.9 to 8.9) in patients who received placebo. The HR for death was 0.56 (95% CI 0.39 to 0.81; p=0.0011). Grade 3/4 neutropenia occurred in 50% of TAS-102-treated patients and no patients who received placebo. Leucopenia occurred in 28% and anaemia in 17% of TAS-102-treated patients compared with 3% of placebo patients who had grade 3 anaemia. Serious adverse events occurred in 19% of patients in the TAS-102 group and in 9% of placebo patients.

Comment (JS): Another new drug for advanced CRC? Hot on the heels of positive trials with regorafenib and aflibercept is this Lancet publication of a Japanese randomised phase II study reporting significant clinical activity for TAS-102, a previously unheralded designer oral fluoropyrimidine. Study patients were refractory to all standard therapies and received either TAS-102 or matched placebo in a 2:1 randomisation. A statistically significant improvement in median OS (9.0 vs 6.6 months), median PFS (2.0 vs 1.0 months), and disease control (43% vs 11%) were reported with TAS-102 vs placebo. Interestingly, patients with a *KRAS* mutation appeared to derive greater benefit (HR for OS 0.44 vs 0.70 for wild-type), although numbers were small. The reproducibility of this encouraging effect is currently being tested in a large multi-national phase III trial. Dosing also needs further study with phase I studies in USA resulting in a lower recommended dose than used in Japan (25 mg/m^2 vs 35 mg/m^2 twice daily) despite similar pharmacokinetic profiles.

Reference: Lancet Oncol 2012;13(10):993-1001
http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(12)70345-5/fulltext

Natural history of bone metastasis in colorectal cancer: final results of a large Italian bone metastases study

Authors: Santini D et al

Summary: This retrospective observational study surveyed the natural history of bone metastasis in 264 patients with CRC. Most patients with bone metastases had pathologic T3/4 disease at CRC diagnosis. Median time from CRC diagnosis to bone metastasis was 11 months, median time to first skeletal-related event after bone metastasis was 2 months, and median survival after bone metastasis was 7 months. Skeletal-related events did not significantly affect survival. The most common site involved was the spine (65%), then the hip/pelvis (34%), long bones (26%) and other sites (17%). Radiation affected 45% of patients and 10% had pathologic fractures; 32% of patients had no skeletal-related events. Subgroup analyses showed zoledronic acid significantly prolonged median time to first skeletal-related event by 1 month (p=0.009) and trended to improve overall survival compared with no zoledronic acid. The authors concluded that their study 'illustrates the burden of bone metastases from CRC and supports the use of zoledronic acid in this setting.'

Comment (JS): This retrospective Italian observational study collecting data on 2500 patients in 16 centres over 24 years highlights the poor prognosis of colorectal cancer patients with skeletal metastases. Bone metastases are present in 10% of metastatic CRCs at diagnosis. Patients with bone metastases fare poorly, with median survival of only 7 months after bone metastases are documented, and with first skeletal-related event at a median of only 1 month after diagnosis. A similar aggressive course has recently also been reported for patients with metastatic renal cancer who have skeletal metastases. Further subgroup analysis suggested zoledronic acid use prolonged time to first skeletal-related event and trended to a survival benefit, although this difference could also be due to patient selection (more advanced patients may have been less likely to have been offered zoledronic acid). Australian CRC patients are not able to access this or similar bone protective therapies currently on the PBS.

Reference: Ann Oncol 2012;23(8):2072-2077
http://annonc.oxfordjournals.org/content/23/8/2072.abstract

Cetuximab rechallenge in metastatic colorectal cancer patients: how to come away from acquired resistance?

Authors: Santini D et al

Summary: This phase II study investigated the activity of retreatment with cetuximab-based therapy in 39 patients with metastatic CRC refractory to irinotecan. All patients had a clinical benefit after a line of cetuximab- plus irinotecan–based therapy and then a progression of disease. They then underwent a new chemotherapy and after new progression of disease were retreated with the same cetuximab- plus irinotecan-based therapy they were treated with previously. The median interval between the last cycle of first cetuximab-based therapy and first cycle of retreatment was 6 months. Overall response rate was 53.8%, with 48.7% partial response and 5.1% complete response. Disease stabilisation was obtained in 35.9% of patients, while 10.2% progressed. Median progression-free survival was 6.6 months. There was a significant correlation between skin toxicity during first cetuximab therapy and during cetuximab rechallenge (p=0.01). The authors concluded that 'rechallenge with the same cetuximab-based therapy may achieve a new important clinical benefit further delaying the progression of disease and improving therapeutic options.'

Comment (JS): This is an interesting paper that challenges the well-accepted dogma that patients who progress on a particular chemotherapy regimen would be most unlikely to benefit from subsequent retreatment with the same treatment. In this study, irinotecan- and cetuximab-refractory patients, who progressed after another line of chemotherapy, appeared to derive substantial clinical benefit (49% partial response and 5% complete response) when retreated with the same irinotecan + cetuximab regimen. All these patients had initially progressed on irinotecan prior to first use of the irinotecan + cetuximab combination, and all had documented progression after irinotecan + cetuximab and then the subsequent chemotherapy regimen (mostly FOLFOX), with a median interval between cetuximab regimens of 6 months. No convincing argument was put by the authors to explain this most surprising finding.

Reference: Ann Oncol 2012;23(9):2313-2318
http://annonc.oxfordjournals.org/content/23/9/2313.abstract

Yttrium-90 radioembolization as salvage therapy for colorectal cancer with liver metastases

Authors: Martin LK et al

Summary: This retrospective study assessed the efficacy of yttrium-90 radioembolisation in 24 patients with unresectable CRC with liver metastases. All patients had refractory disease and had received a median of three prior therapies. Extrahepatic disease was evident in 54% of patients and 67% had bilobar involvement. No patients had an objective response, but five patients had a CEA response. Median PFS was 3.9 months (95% CI 2.4 to 4.8) and median OS was 8.9 months (95% CI 4.2 to 16.7). PFS and OS were improved in patients older than 65 years compared with younger patients. The authors suggested this was likely due to receipt of yttrium-90 treatment earlier in their disease course. Negative predictors of efficacy included presence of extrahepatic disease and absence of a CEA response.

Comment (JS): Here is another small (24 patients) single-institution series describing the use of SIRT in chemorefractory advanced CRC patients. This series is notable for the lack of clinical efficacy – no responders were seen, PFS was short, and although five patients had brief CEA responses, this did not translate into a survival benefit for these patients. At least the toxicity reported was mild, although 10% developed gastric ulceration.

My reason for selecting this report is to highlight the often poor selection of patients undergoing SIRT (as also reflected in this study), which may well have contributed to these poor results. Half of the patients had extrahepatic disease, and of the 67% with bilobar liver disease, only 17% had both lobes appropriately treated with SIRT. What then is the role for SIRT, which despite countless retrospective series and enthusiastic marketing, still has minimal randomised data to support its use? In the chemo-refractory setting, restricting treatment to those with liver-predominant or liver-only disease, which can all be appropriately and safely encompassed, is surely an important first step. Collecting quality-of-life data in this patient subgroup is also clearly important, yet has been neglected to date.

Much will hinge on the results of the nearly completed randomised phase III trials evaluating the addition of SIRT to first-line chemotherapy (SIRFLOX and FOXFIRE). To include SIRT in standard treatment algorithms, we would need to see a meaningful gain in overall survival (rather than just increasing response, lowering CEA, and delaying hepatic recurrence).

Reference: Clin Colorectal Cancer 2012;11(3):195-199
http://www.clinical-colorectal-cancer.com/article/S1533-0028(11)00171-X/abstract

Molecular pathways in colorectal cancer

Authors: Al-Sohaily S et al

Summary: This review discusses the genetic basis of hereditary CRC and the different pathways involved in the process of colorectal carcinogenesis. It focuses on three molecular pathways of genomic instability that have been identified: chromosomal instability, microsatellite instability and the CpG Island Methylator Phenotype. Some tumours may exhibit features of multiple pathways. The review includes discussion of hereditary CRC syndromes, which account for <5% of all CRCs, and the germline mutations involved, as well as the genetic and epigenetic alterations involved in sporadic CRC.

Comment (ES): This is an excellent review article in the 'Mechanisms of disease' section of this journal. It is written by an internationally recognised Australian translational research group, headed by Professor Andrew Biankin, and describes the current state of knowledge regarding the three main molecular pathways involved in the pathogenesis of CRC. The article covers hereditary CRC syndromes and the sporadic tumours. Like breast cancer, CRC is likely in future to be classified by type of molecular abnormality, so it is worthwhile becoming familiar with the different pathways which may dictate prognosis and may also be predictive of response to future therapies.

Reference: J Gastroenterol Hepatol 2012;27(9):1423-1431
http://onlinelibrary.wiley.com/doi/10.1111/j.1440-1746.2012.07200.x/abstract

Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen

Authors: Van Cutsem E et al

Summary: The addition of aflibercept, a novel anti-angiogenic agent, to FOLFIRI provided a significant survival benefit compared with the addition of placebo to FOLFIRI in this phase III study of 1226 patients with metastatic CRC previously treated with oxaliplatin. Some patients had also received prior treatment with bevacizumab. Patients were randomised to receive aflibercept 4 mg/kg (n=612) or placebo (n=614) every 2 weeks in combination with FOLFIRI. Treatment was continued until disease progression or unacceptable toxicity. Median OS was 13.50 months with aflibercept compared with 12.06 months with placebo (HR 0.817; 95% CI 0.713 to 0.937; p=0.0032). Median PFS was also significantly improved with aflibercept (6.90 vs 4.67 months; HR 0.758; 95% CI 0.661 to 0.869; p<0.0001). Survival benefits with aflibercept were consistent for all subgroups, including patients who had previously received bevacizumab. The response rate in the aflibercept group was 19.8% (95% CI 16.4% to 23.2%) compared with 11.1% (95% CI 8.5% to 13.8%) in the placebo group (p=0.0001). Adverse events in the aflibercept group were consistent with anti-VEGF effects and there was also an increased incidence of some chemotherapy-related toxicities.

Comment (JS): Enthusiasm for anti-angiogenic therapy in advanced CRC has been gradually waning since the initial presentations of the Hurwitz and Giantonio papers nearly a decade ago reporting a survival benefit when bevacizumab was added to chemotherapy in first- and second-line metastatic CRC. This is due to subsequent trials showing smaller and inconsistent benefits, although notably still always in favour of bevacizumab.

Momentum may be starting to return. Here is the publication of the first of two recent trials reporting a survival benefit when an angiogenesis inhibitor is added to second-line therapy. In this study, a novel angiogenesis agent, aflibercept (a recombinant fusion protein acting as a ligand trap to block VEGFA,B and PlGF) was able to demonstrate a modest but significant PFS and OS benefit in the second-line setting, when added to FOLFIRI, even in the subgroup of patients who had previously received bevacizumab. In addition to the usual bevacizumab side effects, other tyrosine kinase inhibitor-like toxicities are seen with this agent including hand-foot syndrome, stomatitis, asthenia and cytopenias. The TML study presented by Arnold et al. at ASCO 2012 (http://tinyurl.com/6ntejdp) of bevacizumab beyond first progression produced a survival benefit of similar magnitude (albeit with significant differences in study populations) and adds further weight to the rationale for continuing angiogenesis inhibition into second-line treatment. However given the modest benefit seen, and the significant treatment costs, it will be critical to identify predictive biomarkers to help determine which patients will benefit, and who should continue bevacizumab rather than switch to aflibercept at first progression. This is the subject of the soon to open AIO PERMAD trial which is planned to include Australian centres. The other question raised by this paper is whether continuing an angiogenesis strategy will be superior to switching to an anti-EGFR-targeted agent in patients with *KRAS* wild type.

Reference: J Clin Oncol 2012;30(28):3499-3506
http://jco.ascopubs.org/content/30/28/3499.abstract