Welcome to this review of the 18th European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer, held in Barcelona, Spain. This review has been created to allow those unable to attend, but with a keen professional interest, to access a summary of some of the presentations. Selection and review of the research has been carried out independently by Genni Newnham of St Vincent’s Hospital, Melbourne.

Highlights of this review include an investigation into a useful new assay (BEAMing) for RAS mutation analysis in patients with metastatic colorectal cancer. The assay utilises circulating tumour DNA, potentially avoiding the need for invasive biopsy. For patients with advanced BRAF-mutant colorectal cancer, early data from a phase II study of triplet chemotherapy with encorafenib, cetuximab and alpelisib suggests the combination may have promise. Finally, preliminary results from the GRECCAR-4 study which investigated a tailored management approach to the treatment of patients with locally advanced rectal carcinoma are reported.

We hope you enjoy these selections, and as always, look forward to hearing your comments and feedback.

Kind Regards,

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Biomarker analyses of second-line ramucirumab in patients with advanced gastric cancer from RAINBOW, a global, randomized, double-blind, phase 3 study

Authors: Van Cutsem E et al.

Summary: These researchers collected plasma samples prior, during and after treatment from all participants in the placebo-controlled RAINBOW trial of ramucirumab plus paclitaxel in order to determine whether biomarkers identifying patients with advanced gastric cancer who were responsive to ramucirumab therapy could be identified; potential prognostic biomarkers were also investigated. Candidate biomarkers included VEGF-C and -D, sVEGFR 1, 2 and 3 and platelet derived growth factor. No relationships after treatment from all participants in the placebo-controlled RAINBOW trial of ramucirumab plus paclitaxel in order to determine whether biomarkers identifying patients with advanced gastric cancer who were responsive to ramucirumab therapy could be identified; potential prognostic biomarkers were also investigated. Candidate biomarkers included VEGF-C and -D, sVEGFR 1, 2 and 3 and platelet derived growth factor. No relationships between the molecules studied and OS or PFS with ramucirumab therapy were identified. However biomarkers with potential prognostic value in advanced gastric cancer (longer OS or PFS using an alpha of 0.05) included CRP, hepatocyte growth factor, ICAM-3, IL-8, serum amyloid A and VEGF-A.

Comment: Surgical resection of non-metastatic pancreatic adenocarcinoma remains the only potentially curative treatment option. Unfortunately the majority of patients have unresectable disease at diagnosis due to the presence of distant metastases or involvement of local structures. For a small proportion of patients, pre-operative treatment may render previously unresectable disease resectable, improving outcomes. Such pre-operative treatment may include chemotherapy, radiotherapy or both. This presentation described the long term results of the SCALOP trial, which enrolled 114 patients between 2009 and 2011. An earlier publication reported increased toxicity and inferior outcomes with gemcitabine-RT, however this more mature data, collected with only 5 surviving patients, describes similar outcomes from both arms. Whilst equivalent between the arms, overall survival remains disappointing at less than 18 months for both arms. It is difficult to determine the clinical significance of this information given the low number of randomised patients (74), and the advent of more active chemotherapy regimens such as gemcitabine/abraxane or FOLFIRINOX since the conduct of this study.

Abstract

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Comment: Ramucirumab is a recombinant antibody to VEGFR-2, with anti-angiogenic effects. Whilst current evidence does not support a role in first-line treatment of gastro-oesophageal carcinoma, it has proven benefit in the second-line setting, either as monotherapy (REGARD trial) or in combination with paclitaxel chemotherapy (RAINBOW trial). This presentation reported results of a search for biomarkers predictive of response to this agent in the RAINBOW study. Unfortunately despite assessing a number of factors, and identifying a number of potential prognostic candidates, none were found to be reliably predictive of response to treatment. So we remain limited in our ability to accurately select patients likely to benefit from anti-angiogenic agents. This limitation, as well as the significant cost associated with this agent makes it difficult to use in Australia.

Abstract

Abbreviations used in this issue:

- CRT = chemoradiotherapy
- (m)CRC = metastatic colorectal cancer
- HR = hazard ratio
- OS = overall survival
- OR = odds ratio
- PFS = progression-free survival

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Abstract

Long-term outcome from the SCALOP trial: a multi-centre randomized phase II trial of gemcitabine or capecitabine-based chemoradiation for locally advanced pancreatic cancer

Authors: Hurt C et al.

Summary: These authors presented long-term outcomes from the SCALOP trial in which patients with locally advanced pancreatic cancer were treated with induction chemotherapy followed by CRT with gemcitabine or capecitabine. From an initial 74 randomised participants, this analysis reported data for 5 surviving patients (capecitabine n = 3/38) with a median follow-up of 12.2 months. Subjects who received capecitabine had median OS of 17.6 months (95% CI; 14.6, 22.7) vs 14.6 for those treated with gemcitabine (11.1, 16.0); HR 0.73 (0.46, 1.18; p = 0.203), adjusted HR 0.67 (0.38, 1.21; p = 0.185). Respective rates for median PFS were 12.0 months (10.0, 15.2) vs 10.4 months (8.8, 12.7); HR 0.73 (0.44, 1.23; p = 0.244), adjusted HR 0.60 (0.32, 1.14; p = 0.120). Under multivariable analysis by baseline characteristics, factors associated with improved OS amongst all 114 recruited patients were age ≥ 65 years (p = 0.0013), WHO performance score 0 (p < 0.001 vs performance score 1-2), cancer antigen 19-9 < 613 (p < 0.001) and smaller tumour diameter (p = 0.005).

Comment: Surgical resection of non-metastatic pancreatic adenocarcinoma remains the only potentially curative treatment option. Unfortunately the majority of patients have unresectable disease at diagnosis due to the presence of distant metastases or involvement of local structures. For a small proportion of patients, pre-operative treatment may render previously unresectable disease resectable, improving outcomes. Such pre-operative treatment may include chemotherapy, radiotherapy or both. This presentation described the long term results of the SCALOP trial, which enrolled 114 patients between 2009 and 2011. An earlier publication reported increased toxicity and inferior outcomes with gemcitabine-RT, however this more mature data, collected with only 5 surviving patients, describes similar outcomes from both arms. Whilst equivalent between the arms, overall survival remains disappointing at less than 18 months for both arms. It is difficult to determine the clinical significance of this information given the low number of randomised patients (74), and the advent of more active chemotherapy regimens such as gemcitabine/abraxane or FOLFIRINOX since the conduct of this study.

Abstract

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Abstract
MSCMCC gastric cancer cohort: indirect comparison between adjuvant chemoradiation and perioperative chemotherapy in gastric cancer patients in a referral site

Authors: Mydlowska M et al.

Summary: This retrospective before and after study utilised the medical records of patients with gastro-oesophageal carcinoma undergoing gastrectomy to compare two alternative treatment strategies. Subjects had undergone gastrectomy between 2011 and 2014; those treated during 2011-2012 received adjuvant CRT (n = 46), whereas those treated after January 2013 received perioperative chemotherapy (n = 37). During median follow-up of 50 months for CRT and 27 months with chemotherapy, disease-free survival rates were similar; the proportion of participants remaining relapse-free at two years was 55 and 62% respectively. Both regimens had similar toxicity profiles, with no differences in rates of neutropenia, anaemia or mucositis; CRT recipients reported more leucopenia (41 vs 19%; p = 0.029) whereas more chemotherapy recipients experienced vomiting (32 vs 13%; p = 0.033).

Comment: The addition of either preoperative CRT or perioperative cisplatin-based chemotherapy is known to improve outcomes in resectable gastro-oesophageal carcinoma. However the two approaches have not been directly compared and uncertainty remains regarding which is the preferred approach. In clinical practice the choice is usually made based on personal preference of the treating surgeon and oncologist(s). Such personal preferences are often strongly held and may limit enrolment into randomised studies. This is an interesting report comparing outcomes between the two approaches in a single centre where practices changed in 2013. It appears that there is no difference in 2 year disease-free survival between the two approaches, however longer follow-up is required to compare OS. Obviously randomised data is preferred to retrospective data over differing time periods, however it has been historically very difficult to enroll to such studies, and it may be that comparisons such as this are the best information we will have. For now it seems reasonable to accept either CRT or chemotherapy in this setting, however if OS differences are seen with longer follow-up perhaps renewed attempts at randomised studies would be called for.


Observational data outcomes of chemotherapy backbone in MSI – high metastatic colorectal cancer in Israel

Authors: Schulman K et al.

Summary: This Israeli analysis utilised data from the population-based Molecular Epidemiology of Colorectal Cancer (MECC) study to examine outcomes for patients treated for microsatellite-stable (MSI) colorectal cancer. Amongst a total cohort of 551 patients, 87 had MSI-high tumours. Oxaliplatin-based/bevacizumab regimens were associated with numerically superior OS vs 5-FU monotherapy in MSI-high patients but differences were not statistically significant. Patients with MSI-high/BRAF-negative tumours had similar OS whether treatment was with irinotecan/oxaliplatin/bevacizumab or 5-FU/LV only (HR 0.97; p for interaction = 0.035), however those with MSI-stable/BRAF-negative disease had a more favourable response to irinotecan/oxaliplatin/bevacizumab (HR 0.94; p < 0.01).

Comment: Deficiency of mismatch repair (MMR) genes results in the accumulation of DNA abnormalities known as microsatellites, and an overall increased genetic instability, sometimes referred to as microsatellite instability (MSI). MSI is seen in tumours of patients with HNPCC or Lynch syndrome, and can also occur in approximately 15% of sporadic CRCs. The presence of MMR deficiency/MSI in early stage CRC is associated with a characteristic phenotype (right sided, mucinous tumours), improved prognosis, and reduced benefit from 5-FU-based chemotherapy. However MMR deficiency/MSI is reported as occurring infrequently in metastatic CRC, and has been linked with poor prognosis, possibly due to a higher rate of BRAF mutation. The implications of MSI on treatment in advanced CRC are less clear, however recent evidence suggests this may be a group that will benefit from checkpoint inhibition. This presentation described the frequency, association and treatment outcomes of a group of patients with MSI tumours, taken from database records in Israel. They report an MSI incidence of almost 20%, with reduced benefit from more intensive chemotherapy in MSI tumours. These results remind us of the importance of assessing for MSI in both early stage and metastatic CRC, and incorporating results into treatment decisions when possible. Referral of these patients to clinical studies of immune agents would seem prudent.


Response to chemotherapy and prognosis in metastatic colorectal cancer with deficient mismatch repair

Authors: Alex A et al.

Summary: This case-control study compared chemotherapy response rates (RECIST 1.1) in mCRC patients with DNA deficient mismatch repair (dMMR, n = 41) and controls with proficient MMR (pMMR, n = 84); the proportion of subjects with dMMR amongst the screened cohort was 3.5%. Response rates to oxaliplatin-based chemotherapy were 9.7% in cases vs 28.6% in controls (OR 0.27: 95% CI; 0.07, 0.91; p = 0.032), and were higher (16%) in those with probable Lynch dMMR vs those with sporadic dMMR (0%). An association between BRAF mutation and dMMR was observed, and this had prognostic significance in the sporadic group; 29.8 vs 5.9 months (p = 0.025).

Comment: As described in the previous review, dMMR in resected CRC has been linked with improved prognosis and relative chemotherapy resistance. The clinical implications of dMMR in mCRC are less clear. This case-control study comparing response rates to oxaliplatin-based chemotherapy in patients with dMMR mCRC to those with pMMR describes a much lower frequency of dMMR than that reported in the study by Schulman et al. However like that study, this group report significantly lower response rates to oxaliplatin-based chemotherapy in patients with dMMR mCRC. This apparent chemoresistance combined with reports of others of sensitivity to immunotherapy in dMMR CRC adds to the building evidence that dMMR CRC possesses important behavioural differences to pMMR CRC which need to be taken into account when making treatment decisions.


Circulating tumor DNA extended RAS mutational analysis as a surrogate of mutational status of tumor samples in metastatic colorectal cancer and its impact on patient selection for anti-EGFR therapy

Authors: Grasselli J et al.

Summary: This study assessed the utility of the BEAMing (Beads, Emulsions, Amplification, Magnetics) assay for RAS mutation testing of circulating tumour DNA (ctDNA) from plasma in comparison to standard of care qPCR of tumour biopsies. Samples from plasma and biopsies were collected at the time of diagnosis with mCRC (n = 147) and prior to treatment with EGFR monoclonal antibodies. Use of the BEAMing technique resulted in RAS positivity concordance of 89.2% (k = 0.83: 95% CI; 0.74, 0.92) between plasma and tissue samples. Concordance of 89.8% (k = 0.83; 0.81, 0.91) was achieved between BEAMing and qPCR performed on plasma or tissue samples respectively, and of 90.8% (k = 0.83, 0.74, 0.92) between the two techniques when both were performed on tissue samples.

Comment: The importance of RAS mutation in predicting insensitivity to EGFR monoclonal antibodies in mCRC is well recognised. Current standard testing methods require tumour tissue for analysis. There is increasing interest in the detection of circulating tumour cells and ctDNA and the potential prognostic and predictive applications of these techniques. These presenters reported their results comparing a new technique of RAS analysis (BEAMing) performed on both plasma and tumour tissue to those from standard qPCR or pyrosequencing of tumour tissue. Their results support the feasibility of ctDNA detection and analysis for RAS mutation in mCRC. The potential clinical implications of such techniques are vast. With increasing experience one can be hopeful that numerous predictive and prognostic biomarkers could be identified in plasma, removing the need for invasive biopsy, allowing safe serial assessments, and accurately guiding treatment for patients with malignancy.


Independent commentary by Dr Genni Newnham (MBBS (Hons), MD, FRACP)

Genni is a medical oncologist based at St Vincent’s Hospital, Melbourne. Her particular interests include cancers of the lung and GI tract. Genni graduated from The University of Melbourne in 1997. After obtaining her Fellowship, she went on to complete a lab-based MD thesis on molecular analysis of non-small cell lung cancer.
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Combination of encorafenib and cetuximab with or without alpelisib in patients with advanced BRAF-mutant colorectal cancer

Authors: Tabernero J et al.

Summary: This presentation reported phase II results of an ongoing phase II clinical trial which compared triplet (encorafenib, cetuximab, alpelisib, n = 52) and doublet (encorafenib plus cetuximab, n = 50) chemotherapy in subjects with advanced BRAF-mutant CRC who had failed at least one prior line of therapy. In a planned analysis conducted after 73 events, triplet chemotherapy resulted in a median PFS (primary outcome measure) of 5.4 months (95% CI: 4.1, 7.0) vs 4.2 months (3.4, 5.4) with doublet chemotherapy: HR 0.69 (0.43, 1.11; p = 0.064). The overall response rate was 27% (16, 41) vs 22% (12, 36) with triplet and doublet therapy respectively. Respective rates for disease control were 79% (65, 89) vs 78% (64, 89). Reported rates of grade 3/4 adverse events with triplet therapy were 79% compared to 58% with doublet therapy. Respective rates of grade 3/4 adverse events experienced by > 10% of patients (either arm) were 17 vs 6% for anaemia, 13 vs 2% for hyperglycaemia and 8 vs 18% for increased lipase.

Comment: Although conflicting data exists, the bulk of evidence suggests that BRAF-V600E activating mutation is associated with poorer prognosis in both early stage and metastatic CRC. The mutation is uncommon, being found in less than 10% of CRC, however is seen more commonly in mismatch repair deficient mCRC. Unlike metastatic melanoma, the use of specific BRAF inhibitors in BRAF-mutant mCRC has not resulted in improved outcomes possibly due to activation of alternative pathways. The data presented here is interim data relating to a phase II/III study which is ongoing. The rationale involves simultaneous blockade of either 2 or 3 molecular pathways implicated in oncogenesis and survival of mCRC - BRAF (encorafenib), EGFR (cetuximab) and PI3K (alpelisib) pathways. This approach shows promising initial results, with increased toxicity seen in the triplet arm. Further studies are required to determine if these combinations will provide meaningful clinical improvements for patients.


Association between chemotherapy-induced neutropenia at 1-month and overall survival in patients receiving TAS-102 for metastatic colorectal cancer

Authors: Kotani D et al.

Summary: These authors conducted a retrospective cohort study in order to investigate potential associations between favourable outcomes in patients with chemotherapy-induced neutropenia (CIN) treated with TAS-102 (trifluridine/tipiracil hydrochloride). Subjects were 149 patients with mCRC who received TAS-102 monotherapy at a single centre between May 2014 and September 2015. Grade 2 or higher CIN occurred in 46% of participants at 1 month and was associated with improved median PFS (HR 0.21; 95% CI: 0.11, 0.38) and OS (14.0 vs 5.6 months; log-rank P value < 0.0001). Independent predictors of OS were CIN ≥ grade 2 at 1 month (adjusted HR 2.01; 95% CI: 0.11, 0.38) and higher baseline carcinoembryonic antigen levels (adjusted HR 2.00: 1.22, 3.35).

Comment: TAS-102 is a novel oral anticancer agent consisting of the nucleoside analogue trifluridine, combined with the thymidine phosphorylase inhibitor tipiracil hydrochloride. In the RECOURSE study TAS-102 provided survival benefit when compared to placebo and best supportive care in pretreated mCRC. Continued exposure results in trifluridine incorporation into tumour cell DNA and subsequent anti-tumour effects. It is believed that trifluridine also accumulates in the DNA of leukocytes, with resultant neutropenia. These investigators report their retrospective review of 149 patients treated with TAS-102. They describe improved PFS and OS for patients with grade 2 or higher neutropenia at 1 month from commencing treatment, and suggest that this could be used as a predictive marker of response. If this finding is supported by others, it would then be interesting to determine whether dose adjustment to cause neutropenia can alter outcomes.


The relationship of high neophilutoph-to-lymphocyte ratio to disease-free survival in colorectal cancer

Authors: Mouchli Mohamed A et al.

Summary: This study aimed to examine the prognostic utility of the neutrophil to lymphocyte ratio (NLR) in patients with CRC. Subjects were consecutive Mayo Clinic patients who received treatment for stage I to III CRC between January 2004 and December 2014 (n = 3,542); the proportion of patients at each stage was 25.8, 23.5 and 26.9% respectively. The most appropriate cut-off value for high vs low pre-operative NLR was calculated as 3 using time-dependent receiver operating characteristic curve analysis. Subjects with a high baseline NLR had shorter disease-free survival compared to those with low NLR (P = 0.0001). Independent risk factors which predicted recurrent CRC under multivariate analysis were NLR > 3, number of positive lymph nodes and tumour size, grade and stage.

Comment: Systemic inflammation may play a role in cancer development and progression, through effects on the tumour microenvironment. Readily available methods to quantify the degree of systemic inflammation include assessment of serum CRP and albumin, and NLR. The NLR has been linked with poor prognosis in solid tumours in earlier studies. Results from this retrospective review of over 3,500 patients with early stage colorectal carcinoma support the prognostic value of NLR, with a higher ratio being associated with poorer disease-free survival in all stages of disease. An important next step will be the assessment of the utility and reliability of NLR in guiding treatment selection for patients.


Tailored strategy for locally-advanced rectal carcinoma

Authors: Roussel P et al.

Summary: These authors presented preliminary results from the GRECCAR-4 study, a phase II, multicentre, randomised trial which aimed to evaluate a tailored management approach for patients with locally advanced rectal adenocarcinoma (LARC). 206 subjects with LARC (T3 ≥ c; T4 predictive of lymph node involvement, N1, N2) were treated with CIN ≥ grade 2 at 1 month from commencing treatment, and suggest that this could be used as a predictive marker of response. If this finding is supported by others, it would then be interesting to determine whether dose adjustment to cause neutropenia can alter outcomes.