Oncology Research Review™

Making Education Easy

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Abbreviations used in this review:

AE = adverse event; **CRC** = colorectal carcinoma; **CRM** = circumferential resection margin; **EGFR** = epidermal growth factor receptor; **ER** = oestrogen receptor; **HER2** = human epidermal growth factor receptor 2; **HRQoL** = health-related quality of life; **mCRC** = metastatic colorectal carcinoma; **mrEMVI** = extramural venous invasion identified on magnetic resonance imaging; **MRI** = magnetic resonance imaging; **PFS** = progression-free survival; **PgR** = progesterone receptor; **SRE** = skeletal-related event; **ZA** = zoledronic acid

Welcome to the eighteenth issue of Oncology Research Review.

As one of the papers in this issue testifies, discordance between the status of primary breast cancer and metastases occurs in a significant number of cases. Some oncologists believe that biopsy of metastases should be considered as part of routine management of recurrences in order to optimise treatment plans.

Another paper reports that patients who developed some form of cardiotoxicity with a variety of fluoropyrimidine-containing regimens and who then switched to treatment with raltitrexed, a direct inhibitor of thymidine synthase, experienced no further cardiac problems. This evidence has important implications for clinical practice.

I hope you find the research in this edition useful to you in your practice and I welcome your comments and feedback.

Kind Regards,

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A meta-analysis of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 discordance between primary breast cancer and metastases

Authors: Aurilio G et al.

Summary: Evidence was assessed from 48 studies published between 1983 and 2011 comparing changes in oestrogen receptor (ER), progesterone receptor (PgR) and/or human epidermal growth factor receptor 2 (HER2) status in patients with matched breast primary and recurrent tumours. A total of 4200, 2739 and 2987 tumours were evaluated for ER, PgR and HER2 discordance, respectively. The heterogeneity between study-specific discordance proportions was high for ER (I^2=91%, p<0.0001), PgR (I^2=79%, p<0.0001) and HER2 (I^2=77%, p<0.0001). Pooled discordance proportions were 20% for ER, 33% for PgR and 8% for HER2. Pooled proportions of tumours shifting from positive to negative and from negative to positive were 24% and 14% for ER (p=0.0183), respectively, 46% and 15% for PgR (p<0.0001) and 13% and 5% for HER2 (p=0.0004), respectively.

Comment: With increased understanding of breast cancer biology, the importance of molecular features such as ER, PR and Her2 status in predicting outcomes and directing treatment is becoming apparent. Whilst it is not standard practice to re-biopsy sites of metastatic disease, there are some who would recommend it be so. A number of papers have reported discordance between the molecular features of primary and metastatic tumours. Obviously, such discordance could have serious implications for treatment efficacy.These authors performed a meta-analysis of available studies examining such molecular discordance in breast cancer. The reported rates of both positive and negative conversion for the three markers in question cannot fully be explained by technical factors and almost certainly represent subpopulations or clonal evolution of cancer cells. The clinical utilisation of this concept is one of debate. Tumour biopsy is not without morbidity and can be anxiety-provoking for patients. Clearly, clinical judgement is required to determine the most appropriate timing for re-biopsy (e.g., late metastasis, mixed disease response, early and/or frequent treatment failures), but it should be considered.

Reference: Eur J Cancer. 2014;50(2):277-89.
http://www.ejcancer.com/article/S0959-8049(13)00904-0/abstract

Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD)

Authors: Fuchs CS et al.

Summary: This phase 3 trial enrolled 355 patients aged 24–87 years with advanced gastric or gastro-oesophageal junction adenocarcinoma and disease progression after first-line platinum-containing or fluoropyrimidine-containing chemotherapy and randomised them to receive best supportive care plus either ramucirumab 8 mg/kg (n=238) or placebo (n=117), intravenously once every 2 weeks. The primary endpoint, median overall survival (OS), was significantly prolonged with ramucirumab compared with placebo (5.2 months vs 3.8 months; (hazard ratio [HR] 0.776; p=0.047). This survival benefit with ramucirumab remained unchanged after multivariable analysis adjusting for other prognostic factors (multivariable HR 0.774; p=0.042). Adverse event (AE) rates were higher for hypertension with ramucirumab than with placebo (16% vs 8%), but mostly similar between groups for all other AEs (94% vs 88%). Five (2%) deaths in the ramucirumab group and 2 (2%) in the placebo group were attributed to study drug.

Comment: See below.

Reference: Lancet. 2014;383(9911):31-9.
http://tinyurl.com/m5tkp5o

Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02)

Authors: Ford HER et al.

Summary: This paper presents the final analysis of the open-label, phase 3 COUGAR-2 trial, in which 168 patients aged ≥18 years with an advanced, histologically confirmed adenocarcinoma of the oesophagus, oesophagogastric junction, or stomach that had progressed on or within 6 months of treatment with a platinum-fluoropyrimidine combination were randomised to receive docetaxel (75 mg/m^2 by IV infusion every 3 weeks for up to 6 cycles) plus active symptom control (n=84), or active symptom control alone (n=84). After a median 12-month follow-up and 161 deaths (80 in the docetaxel group, 81 in the active symptom control group), median OS was 5.2 months with docetaxel versus 3.6 months with active symptom control alone (HR 0.67; p=0.01). Docetaxel resulted in a higher incidence of grade 3–4 neutropenia (15% patients vs no patients), infection (19% patients vs 3% patients) and febrile neutropenia (7% patients vs no patients). Significantly fewer patients receiving docetaxel reported pain (p=0.0008), nausea and vomiting (p=0.02) and constipation (p=0.02). Global health-related quality of life (HRQoL) was similar between the groups (p=0.53). Disease-specific HRQoL measures favoured docetaxel (reductions in dysphagia and abdominal pain; p<0.05 for both comparisons).

Comment: Advanced oesophagogastric carcinoma accounts for a substantial proportion of cancer mortality worldwide. Standard first-line treatment with cytotoxic chemotherapy results in median OS in the order of 8–12 months. Treatment options for those progressing after adjuvant or first-line chemotherapy are limited, with little randomised data available. The COUGAR-02 authors investigated the utility of docetaxel as second-line treatment, bearing in mind the need to balance adverse effects with treatment benefit. In a population representative of most standard Western oncology practices, including patients with carcinoma of the oesophagus, gastro-oesophageal junction and stomach, with an Eastern Cooperative Oncology Group performance status of 0–2, they report improved OS with docetaxel. Importantly, despite some toxicities, there was no significant difference in HRQoL between those receiving docetaxel and those receiving supportive care alone. Although patient numbers were small and the absolute survival benefit less than 2 months, this data is sufficient to support the use of docetaxel in second-line. Angiogenic pathways involving vascular endothelial growth factor (VEGF) and VEGFRs have been implicated in gastric carcinoma as supported by animal models and preclinical studies. Ramucirumab is a fully humanised monoclonal antibody targeting VEGF receptor-2 (VEGFR-2). The authors of the REGARD study demonstrated improved median OS using ramucirumab in patients with previously treated advanced gastric/gastro-oesophageal junction carcinoma. As with the COUGAR-02 study, absolute benefits were modest at best but comparable to studies of second-line cytotoxic therapy in similar patients, and seemed to come without undue adverse effects. Important future directions should include assessment of the effect of combined cytotoxic and antiangiogenic treatments, as well as a search for predictive biomarkers.

Reference: Lancet Oncol. 2014;15(1):78-86.
http://tinyurl.com/k2vkamp

Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study

Authors: Taylor FG et al.

Summary: This follow-up study of 374 patients with rectal cancer examined the relationship between preoperative magnetic resonance imaging (MRI) assessment of circumferential resection margin (CRM) staging, American Joint Committee on Cancer (AJCC) TNM stage, and clinical variables with OS, disease-free survival (DFS), and time to local recurrence (LR). Patients underwent protocol high-resolution pelvic MRI. Tumour distance to the mesorectal fascia of ≤1 mm was recorded as an MRI-involved CRM. The 5-year OS was 62.2% in patients with MRI-clear CRM versus 42.2% in patients with MRI-involved CRM (HR 1.97; 95% CI, 1.27 to 3.04; p<0.01); corresponding values for 5-year DFS were 67.2% and 47.3%, respectively (HR 1.65; 95% CI, 1.01 to 2.69; p<0.05). Local recurrence HR for MRI-involved CRM was 3.50 (95% CI, 1.53 to 8.00; p<0.05). In adjusted multivariate analysis, MRI-involved CRM was the only preoperative staging parameter that remained significant for OS, DFS, and LR.

Comment: See below.

Reference: J Clin Oncol. 2014;32(1):34-43.
http://jco.ascopubs.org/content/32/1/34.abstract

Extramural venous invasion is a potential imaging predictive biomarker of neoadjuvant treatment in rectal cancer

Authors: Chand M et al.

Summary: These researchers retrospectively examined the staging and post-treatment MRIs of 62 patients who had presented with extramural venous invasion (EMVI)-positive rectal cancer. All patients had undergone neoadjuvant chemoradiotherapy (CRT) and curative surgery. Changes in EMVI identified on MRI (mrEMVI) were graded with a new MRI-based TRG scale (mr-vTRG). Of 35 patients with >50% fibrosis of mrEMVI (mr-vTRG 1-3), 3-year DFS was 87.8% with 9% recurrence. In contrast, 27 patients with <50% fibrosis (mr-vTRG 4-5) had a 3-year DFS 45.8% with 44% recurrence (p<0.0001). On multivariate Cox-regression, only mr-vTRG 4-5 increased risk of disease recurrence (HR 5.748).

Comment: Tumour extension to within 1 mm of the CRM and venous invasion of tumour cells beyond the muscularis propria (EMVI) are recognised poor prognostic factors in rectal carcinoma. However, current guidelines recommend treatment decisions be based on the AJCC TNM stage rather than CRM or EMVI. Both CRM and EMVI can be reliably assessed on MRI or histopathology. Taylor et al. report the 5-year follow-up of the MERCURY study, demonstrating accurate prediction of LR, DFS and OS outcomes with both pathological and/or MRI-assessed CRM (which were not always concordant). The study of Chand et al. reports a predictive and perhaps prognostic role for MRI-assessed regression of EMVI after neoadjuvant chemoradiation for high-risk rectal carcinoma, irrespective of pathological tumour stage. These results call into question the current practice of basing neoadjuvant treatment decisions on TNM staging. Perhaps patient selection would be improved by using CRM and/or EMVI to direct neoadjuvant and adjuvant treatment. The ability of different radiologists to consistently report and rate MRI-assessed CRM, EMVI and EMVI regression presents a potential obstacle to this method of treatment selection, and requires further validation. Also of interest for further investigation will be the stratification of treatment based on CRM and/or EMVI regression. What is yet to be determined is whether additional treatment for those deemed at high risk will improve prognosis. Could patient selection using these criteria identify a group who would consistently benefit from adjuvant oxaliplatin (or even 5FU-based) chemotherapy, as benefit from adjuvant chemotherapy in rectal carcinoma is certainly less clear than for colon carcinoma? It is interesting to note that all patients in the EMVI study received adjuvant oxaliplatin-based chemotherapy for rectal carcinoma – a practice that is not routine in this country.

Reference: Br J Cancer. 2014;110(1):19-25.
http://www.nature.com/bjc/journal/v110/n1/abs/bjc2013603a.html

Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: Prespecified subgroup analyses from the VELOUR trial

Authors: Tabernero J et al.

Summary: This paper reports on treatment effects across specified patient subgroups in the phase 3 VELOUR trial, in which patients with metastatic colorectal cancer (mCRC) previously treated with an oxaliplatin-based regimen were randomised to receive 5-fluorouracil, leucovorin and irinotecan (FOLFIRI) plus aflibercept or placebo every 2 weeks until disease progression or unacceptable toxicity occurred. In patients with prior bevacizumab treatment, median OS was 12.5 months with aflibercept and 11.7 months with placebo; corresponding values in patients with no prior bevacizumab treatment were 13.9 months and 12.4 months, respectively. The p value for interaction was 0.5668, indicating there was no heterogeneity in these subgroups. For OS and progression-free survival (PFS), there was a significantly greater benefit of treatment for patients with liver-only metastases versus patients with no liver metastases/liver metastases with other organ involvement (p value for interaction: 0.0899 [OS]; 0.0076 [PFS]). There was no evidence of heterogeneity in treatment effect in any of the other subgroups examined.

Comment: Over half of all patients with CRC have locally advanced or metastatic disease at diagnosis. Several advances have been made in the treatment of advanced CRC in recent years, including the addition of antiangiogenic agents to chemotherapy. The use of bevacizumab in both first- and second-line treatment confers a survival benefit. Aflibercept is a recombinant fusion protein that binds VEGF-A, VEGF-B and placental growth factor, preventing activation of their usual receptors with a subsequent antiangiogenic effect. The VELOUR study reported improvements in both OS and PFS with the addition of aflibercept to FOLFIRI in oxaliplatin-pretreated CRC patients. This paper reports the results of prespecified subgroup analyses. The findings suggest that although the absolute improvements in OS and PFS are small, they are consistent in all patient subgroups, and this combination should be considered a viable treatment option in pre-treated patients, even those who have received bevacizumab.

Reference: Eur J Cancer. 2014;50(2):320-31.
http://www.ejcancer.com/article/S0959-8049(13)00853-8/abstract

Occurrence and survival of synchronous pulmonary metastases in colorectal cancer: A nationwide cohort study

Authors: Nordholm-Carstensen A et al.

Summary: Data from 26,200 patients on the Danish Colorectal Cancer Group's database between May 2001 and December 2011 were combined with data from the Danish Pathology Registry and the National Patient Registry, in this investigation into the occurrence of synchronous CRC metastases (SCCM) confined to the lungs, risk factors for these metastases and their impact on survival. Of 1970 patients identified with pulmonary SCCM, 736 (37%) had metastases confined to the lungs. Advanced age, recent years of diagnosis and a rectal index cancer were significantly associated with pulmonary SCCM. This association remained unchanged after adjusting for excess use of thoracic CT scans in rectal cancer patients (adjusted OR 1.81; 95% CI, 1.46 to 2.25; p<0.001). OS was superior in patients subjected to pulmonary metastasectomy, resection of primary tumour and chemotherapy compared with non-treated patients, especially when these therapeutic modalities were combined.

Comment: The rate of synchronous liver metastases with primary CRC has been reported as ~15%. In a proportion of these patients, curative resection of both primary and metastatic lesions can result in cure. The rate of synchronous CRC metastases confined to the lung is much lower, presumably due to the portal circulation favouring metastases to the liver. As such, outcomes of treatment for pulmonary-only metastases are less well defined. Obviously the group of interest in this study makes up only a small proportion of the patients we see. Nonetheless, the information provided is thought-provoking. This is a retrospective cohort study providing information regarding a group in whom it would be very difficult to conduct a prospective randomised study. Bearing in mind the limitations of this methodology, the data is supportive of an aggressive approach to management, with surgical resection of both primary tumour and pulmonary metastases and the administration of chemotherapy. It also raises the issue of primary tumour resection even in those with residual disease. Other studies have reported improved outcomes with this approach, which remains under debate.

Reference: Eur J Cancer. 2014;50(2):447-56.
http://www.ejcancer.com/article/S0959-8049(13)00936-2/abstract

Oral ibandronic acid versus intravenous zoledronic acid in treatment of bone metastases from breast cancer

Authors: Barrett-Lee P et al.

Summary: This UK trial compared oral ibandronic acid 50 mg/day with IV zoledronic acid (ZA) 4 mg every 3–4 weeks for 96 weeks in the treatment of metastatic breast cancer to bone. The per-protocol analysis included 654 patients in the ibandronic acid group and 672 in the ZA group. The primary non-inferiority endpoint was the frequency and timing of skeletal-related events (SREs) over 96 weeks. Annual rates of SREs were 0.499 with ibandronic acid and 0.435 with ZA (rate ratio 1.148). The upper CI exceeded the predetermined margin of inferiority of 1.08, so the researchers were unable to reject the null hypothesis that ibandronic acid was inferior to ZA. More patients in the ZA group had renal toxic effects than in the ibandronic acid group (32% vs 24%) but rates of osteonecrosis of the jaw were low in both groups (1% vs <1%). The most common grade 3 or 4 AEs were fatigue (14% of ZA recipients vs 14% of ibandronic acid recipients), increased bone pain (13% vs 12%), joint pain (6% vs 5%), infection (5% vs 3%), and nausea or vomiting (5% vs 6%).

Comment: Bisphosphonate therapy in patients with bony metastases from breast or prostate carcinoma has been shown to reduce bone pain and SREs. Zoledronic acid (ZA) has been the bisphosphonate of choice for some time since demonstrating superiority over pamidronate. Nevertheless, ZA has some disadvantages including risks of renal impairment and osteonecrosis of the jaw, as well as the requirement for IV access and nursing time for administration. Ibandronate is an oral bisphosphonate that can be used in the place of ZA. This paper reports the first randomised but unblinded comparison of the efficacy of these two agents in metastatic breast cancer. The results suggest that ZA is superior to ibandronate in preventing SREs in this population, although the differences were small and could possibly be accounted for by reduced compliance with oral ibandronate. One would imagine that this information would guide oncologists to prescribe ZA in preference to ibandronate. However, in situations where concerns exist regarding renal function or where patient convenience is paramount, it would not be unreasonable to use ibandronate. Oncologists should also consider the use of denosumab in preference to both bisphosphonates due to proven superior efficacy and tolerability.

Reference: Lancet Oncol. 2014;15(1):114-22.
http://tinyurl.com/n729sdg

Final results of Australasian Gastrointestinal Trials Group ARCTIC study: an audit of raltitrexed for patients with cardiac toxicity induced by fluoropyrimidines

Authors: Ransom D et al.

Summary: These researchers investigated the incidence of cardiac events in 42 patients who had switched to raltitrexed following cardiac toxicity from fluoropyrimidines (5-fluorouracil or capecitabine). The primary endpoint was the rate of further cardiac events after commencing raltitrexed. Most of the patients had CRC. Prior regimens included 5-fluorouracil ± leucovorin, capecitabine alone, FOLFOX, FOLFIRI, epirubicin/cisplatin/5-fluorouracil, and capecitabine/oxaliplatin. The most frequent cardiotoxicity with 5-fluorouracil or capecitabine was angina and usually occurred in the first or the second cycle. Four patients after their first cardiac event continued with the same 5-fluorouracil or capecitabine regimen with the addition of nitrates and calcium antagonists but still had further cardiac events. After changing to raltitrexed, no further cardiac toxicity developed.

Comment: Fluoropyrimidines such as 5-FU and capecitabine are widely used in the treatment of many malignancies. Cardiac toxicity is an uncommon but potentially life-threatening side effect of these drugs, with a high recurrence rate on rechallenge. Raltitrexed, a thymidylate synthase inhibitor, has been shown in clinical studies to be noninferior to IV 5-FU in the treatment of mCRC, without the reported cardiac risk. This case series of 42 patients in Australia and the UK who switched from 5-FU or capecitabine to raltitrexed after experiencing some form of cardiotoxicity reports a 0% rate of cardiac events after the switch. As the authors well describe, a number of studies have demonstrated equivalence of raltitrexed with bolus 5-FU regimens, and others have demonstrated safety of combining raltitrexed with either oxaliplatin or irinotecan. Whilst the specific comparison of raltitrexed against infusional 5-FU with either oxaliplatin or irinotecan has not been reported, this has little relevance in this group of patients in whom rechallenge with 5-FU carries a high risk and is not recommended. Raltitrexed should be considered a reasonable and safe treatment option in those patients experiencing cardiac toxicity from fluoropyrimidines.

Reference: Ann Oncol. 2014;25(1):117-21.
http://annonc.oxfordjournals.org/content/25/1/117.abstract

Improvements in 5-year outcomes of stage II/III rectal cancer relative to colon cancer

Authors: Renouf DJ et al.

Summary: Disease-specific survival (DSS) and OS were compared for rectal and colon cancer among 1427 patients with resected stage II/III CRC referred to the British Columbia Cancer Agency in 1989/1990 (n=375) and 2001/2002 (n=1052). Significant increases were observed between 1989/1990 and 2001/2002 in the use of perioperative chemotherapy for both rectal and colon cancer ($p<0.001$) and use of preoperative radiation therapy ($p<0.001$) and total mesorectal excision ($p<0.001$) in rectal cancer. DSS significantly improved for rectal ($p<0.001$) but not colon cancer ($p=0.069$). Five-year OS was significantly inferior for rectal versus colon cancer in 1989/1990 (46.1% vs 57.2%; $p=0.023$) and was similar to that of colon cancer in 2001/2002 (63.7% vs 66.2%; $p=0.454$).

Comment: Historically, studies have demonstrated inferior survival outcomes for patients with rectal carcinoma (RC) when compared to stage-matched colon carcinoma (CC). Since 1990, a number of advances have been made in the treatment of RC. In particular, the use of neoadjuvant chemoradiation and total mesorectal excision have both led to improved local control. However, studies of systemic adjuvant therapies in RC have demonstrated less clear survival benefit when compared to that seen in CC. This paper reports outcomes for patients with stage II/III CC and RC treated at the British Columbia Cancer Agency in two distinct time periods, just over 10 years apart. Their findings are consistent with changes in practice that occurred over the period of time examined. The increasing use of neoadjuvant radiotherapy and TME in RC, and perioperative chemotherapy in both CC and RC, resulted in improvements in DSS in RC and OS in CC and RC over time. The survival improvements were limited to patients with stage III disease in both CC and RC, consistent with the documented marginal benefit from adjuvant chemotherapy in stage II CC. Changes in practice have had a greater impact on outcomes in RC than CC resulting in equivalent survival rates between the two entities, also consistent with other recently documented registry data.

Reference: Am J Clin Oncol. 2013;36(6):558-64.
http://tinyurl.com/kk47yqk

