Oncology Research Review™

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In this issue:

Abbreviations used in this issue:

AE = adverse event; **CRC** = colorectal cancer; **CTX** = chemotherapy; **eMBCT** = Internet-based mindfulness-based cognitive therapy; **EGFR** = epidermal growth factor receptor; **FIT** = faecal immunochemical testing; **HR** = hazard ratio; **IHC** = immunohistochemical; **MBCT** = mindfulness-based cognitive therapy; **mCRC** = metastatic colorectal cancer; **mG/GOC** = metastatic gastric/gastro-oesophageal carcinoma; **NBCSP** = National Bowel Cancer Screening Programme; **OS** = overall survival; **PD-1** = programmed cell death; **PD-L1** = programmed cell death ligand 1; **PFS** = progression-free survival; **QALY** = quality-adjusted life year; **RCT** = randomised controlled trial; **TAU** = treatment as usual; **VEGF** = vascular endothelial growth factor.

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Welcome to issue 40 of Oncology Research Review.

One of the papers in this issue reports that a tailored supportive-expressive therapy for patients with advanced cancer appears to relieve and prevent depressive symptoms and help them to address preparations for the end of life. Another paper compares mindfulness-based cognitive therapy and Internet-based mindfulness-based cognitive therapy with treatment as usual in psychologically distressed patients with advanced cancer. Both interventions proved similarly effective at reducing psychological distress and were significantly better than treatment as usual. Both interventions were also superior to treatment as usual for other outcomes including a reduction of psychiatric diagnoses, fear of cancer recurrence and rumination, an improvement in health-related quality of life, mindfulness skills, and positive mental health. The study researchers suggest that for those patients who find it difficult to access clinical appointments for psychological consultations, Internet-based mindfulness cognitive therapy could mean that the patients are more easily able to access such therapy without compromising the effectiveness of the intervention.

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

Kind Regards,

Dr. Genni Newnham

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Efficacy of PD-1 or PD-L1 inhibitors and PD-L1 expression status in cancer: meta-analysis

Authors: Shen X et al.

Summary: This meta-analysis included 8 RCTs and 4,174 patients with advanced or metastatic cancers that were PD-L1-positive or -negative. The studies were identified in the literature or as conference abstracts up to March 2018. The analysis compared the relative efficacies of PD-1 or PD-L1 inhibitors (avelumab, atezolizumab, durvalumab, nivolumab, and pembrolizumab) with those of conventional agents. IHC staining determined the positivity or negativity of PD-L1 expression; PD-L1 stained cell accounted for 1% of tumour cells, or tumour and immune cells. OS was significantly prolonged with PD-1 or PD-L1 inhibitors as compared with conventional agents in the PD-L1-positive (n=2,254; HR 0.66; 95% CI, 0.59 to 0.74) or PD-L1-negative cohorts (n=1,920; HR 0.80; 0.71 to 0.90). Interestingly, the efficacies of PD-1 or PD-L1 blockade treatment differed significantly between patients who were PD-L1-positive and those who were PD-L1-negative (p=0.02). Long-term clinical benefits from PD-1 or PD-L1 blockade were consistent across interventional agent, cancer histotype, method of randomisation stratification, type of IHC scoring system, drug target, type of control group, and median follow-up time, regardless of whether patients were PD-L1-positive or -negative.

Comment: Immune modulation has become the fourth pillar of systemic therapy, along with endocrine, cytotoxic, and targeted therapies. Checkpoint inhibition (CPI) through blockade of PD-1, PD-L1 or CTLA4 has provided the most encouraging results in solid tumours to date. Whilst CPI has provided impressive outcomes for some patients, results for others have been disappointing. Selection of those most likely to benefit remains challenging. IHC staining for PD-L1 has been assessed in many clinical studies of PD-1 and PD-L1 inhibitors, and is used in patient selection for some agents, although is an imperfect selection tool.

These authors report a meta-analysis of studies comparing PD-1 or PD-L1 inhibitors to conventional therapies, in a variety of advanced malignancies. They report improved OS from CPI vs chemotherapy in all studies, with the magnitude of benefit greater for PD-L1-positive than -negative tumours, and clinical benefit regardless of tumour type, IHC scoring system or type of CPI. Whilst encouraging regarding the utility of CPI in advanced malignancy, these results further highlight the inadequacy of PD-L1 IHC staining in selecting those most likely to obtain meaningful benefit. Exploration of alternative or adjunctive selection methods such as tumour mutation burden and other approaches is urgently required.

Reference: BMJ. 2018;362:k3529

Abstract

Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial

Authors: Shitara K et al.

Summary: This multinational trial randomised 592 patients with metastatic gastric/gastro-oesophageal carcinoma (mG/GOC) that had progressed on first-line chemotherapy with a platinum and fluoropyrimidine to receive pembrolizumab 200 mg every 3 weeks for up to 2 years or standard-dose paclitaxel. Primary endpoints were OS and PFS in the 395 patients with a PD-L1 combined positive score (CPS) of ≥1; 196 received pembrolizumab and 199 received paclitaxel. In the cohort with a CPS of ≥1, by 26 October 2017, 326 patients had died (151 [77%] in the pembrolizumab group and 175 [88%] in the paclitaxel group); median OS was 9.1 months with pembrolizumab and 8.3 months with paclitaxel (HR 0.82; 95% CI, 0.66 to 1.03; p=0.0421), while median PFS values were 1.5 months and 4.1 months, respectively (HR 1.27; 95% CI, 1.03 to 1.57). The safety profile was better with pembrolizumab than with paclitaxel; in the total population, grade 3–5 treatment-related AEs were reported in 14% of the pembrolizumab arm compared with 35% of the paclitaxel arm.

Comment: Metastatic gastric/gastro-oesophageal carcinoma (mG/GOC) carries a poor prognosis, with survival rarely exceeding 12 months. Palliative systemic therapy can provide symptom control and modest survival benefit. A number of cytotoxic agents have activity, with better results from combination than monotherapy. There is no globally accepted optimal first-line therapy, and even less certainty about second-line treatment options.

Immunotherapy through PD-1 inhibition has provided impressive results in some patients with other malignancies. Earlier studies in mG/GOC have demonstrated clinical response and survival benefit from PD-1 inhibition in some patients, particularly those with MSI-high or mismatch-repair deficient tumours (consistent with results seen in mCRC). The current study was designed to compare clinical outcomes of pembrolizumab (anti-PD-1 antibody) to paclitaxel chemotherapy in the second-line treatment of mG/GOC. Initially, recruitment did not depend on tumour PD-L1 status, but was later restricted to PD-L1-positive tumours, following interim analysis that suggested inferior results in PD-L1-negative tumours. The final results of this study did not show any survival benefit from the use of pembrolizumab as compared with paclitaxel. Pembrolizumab did have a more favourable safety profile, and post-hoc analysis suggested survival benefit in those with higher tumour PD-L1 scores, although this analysis was not pre-planned and can be considered hypothesis-forming at best. Overall, these results do not support the use of pembrolizumab in this setting. Perhaps with a more selected patient cohort, the results would be more favourable.

Reference: Lancet. 2018;392(10142):123-33
Abstract

Multicenter, randomized, double-blind phase 2 trial of FOLFIRI with regorafenib or placebo as second-line therapy for metastatic colorectal cancer

Authors: Sanoff HK et al.

Summary: This multinational trial enrolled 181 patients (median age, 62 years) with mCRC who progressed on first-line oxaliplatin and fluoropyrimidine and randomised them to receive folinic acid, fluorouracil, and irinotecan (FOLFIRI) on days 1 and 2 and days 15 and 16 with either regorafenib (160 mg; n=120) or placebo (n=61) on days 4 to 10 and days 18 to 24 of every 28-day cycle. Around two-thirds (65%) of the patients had received prior bevacizumab or aflibercept. PFS was prolonged with regorafenib-FOLFIRI (median, 6.1 months vs 5.3 months with placebo-FOLFIRI; p=0.056), but median OS was not (HR 1.01; 95% CI, 0.71 to 1.44). Response rates were higher with regorafenib-FOLFIRI compared with placebo-FOLFIRI (34% vs 21%; p=0.07). Grade 3–4 AEs with a >5% absolute increase from regorafenib included diarrhoea, neutropenia, febrile neutropenia, hypophosphatemia, and hypertension.

Comment: Effective systemic treatment options for mCRC include cytotoxic agents such as oxaliplatin or irinotecan combined with fluoropyrimidine, single-agent fluoropyrimidine, or the combination agent trifluridine/tipiracil, and biologic agents with antiangiogenic or anti-EGFR properties. Evidence regarding the optimal sequencing and combination of available options is conflicting. In practice, either irinotecan or oxaliplatin-based CTX is used first-line for most patients, with the choice based primarily on side effect profile and physician preference. This CTX is often combined with either an anti-VEGF antibody or an anti-EGFR antibody, with selection based on RAS mutation profile, tumour sidedness, and patient co-morbidities. Regorafenib is a small molecule antiangiogenic agent with evidence of modest PFS (1.5 months) and OS (2.5 months) benefit when used as monotherapy in previously treated patients, with moderate toxicity including hand and foot syndrome, fatigue, diarrhoea and risk of liver failure. These authors report minimal benefit from the addition of regorafenib to irinotecan-based chemotherapy in the second-line treatment of mCRC – with a PFS improvement of less than 1 month and a confidence interval crossing 1. This combination cannot be recommended in the second-line treatment of mCRC.

Reference: Cancer. 2018;124(15):3118-26
Abstract

Effectiveness of a mailed colorectal cancer screening outreach program in community health clinics: the STOP CRC cluster randomized clinical trial

Authors: Coronado GD et al.

Summary: US federally qualified health centres have generally low rates of CRC screening. This study examined the effectiveness of an intervention that sought to improve these screening rates. It enrolled 26 federally qualified health centre clinics in Oregon and California that were randomised to usual care (n=13) or a stepwise mailed intervention (n=13) involving (1) an introductory letter, (2) a mailed faecal immunochemical test (FIT), and (3) a reminder letter; training, collaborative learning, and facilitation through a practice improvement process. The study involved 41,193 adults (mean age, 58.5 years; 22,994 women); 20,059 received usual care and 21,134 received standard care and the direct mail colorectal screening intervention. During the study enrolment period (4 February 2014 to 3 February 2015), all participants were overdue for CRC screening. Compared with usual care, the intervention was associated with significantly higher adjusted clinic-level proportions of participants who completed a FIT (13.9% vs 10.4%) and any CRC screening (18.3% vs 14.5%). Effectiveness varied markedly across health centres; net differences in FIT completion ranged from –7.4 percentage points to 17.6 percentage points. Similarly, the proportion of eligible intervention participants who were mailed a FIT ranged from just 6.5% to as many as 68.2% across the centres. The number needed to mail to achieve a completed FIT was 4.8 overall, and 4.0 in clinics that mailed a FIT reminder.

Comment: See adjacent.

Reference: JAMA Intern Med. 2018;178(9):1174-81
Abstract

Comparative effectiveness of mailed reminders with and without fecal immunochemical tests for Medicaid beneficiaries at a large county health department: a randomized controlled trial

Authors: Brenner AT et al.

Summary: Compared with other insured populations, Medicaid beneficiaries have lower CRC screening rates. These researchers examined the feasibility of mailed FIT-based outreach programmes for Medicaid beneficiaries at average CRC risk. An urban health department mailed a CRC screening reminder plus FIT to 1,071 Medicaid beneficiaries, while 1,073 were mailed the same reminder without FIT. The reminder group could request FIT. Respondents were notified of normal results by mail. Abnormal results were delivered by phone call by a patient navigator who provided counselling and assistance with follow-up care. The screening completion rate was significantly higher in the group sent the FIT kit than in group sent a reminder letter alone (21.1% vs 12.3%; p<0.01). Eighteen of the people (7.2%) who completed FIT tests had abnormal results and 15 were eligible for follow-up colonoscopy; 10 completed follow-up colonoscopy.

Comment: See See adjacent.

Reference: Cancer. 2018;124(16):3346-54
Abstract

Family history-based colorectal cancer screening in Australia: a modelling study of the costs, benefits, and harms of different participation scenarios

Authors: Dillon M et al.

Summary: Australia introduced the National Bowel Cancer Screening Programme (NBCSP) in 2006. When fully implemented, people aged 50–74 will be invited by the programme to complete an immunochemical faecal occult blood test (iFOBT) every 2 years. These researchers sought to determine CRC screening occurring outside of the NBCSP. A total of 2,480 participants from the Australasian Colorectal Cancer Family Registry (ACCFR) were classified into 3 risk categories (average, risk category 1; moderately increased, risk category 2; and potentially high, risk category 3) based on CRC family history; screening practices were assessed according to national guidelines. A microsimulation compared hypothetical screening scenarios (70% and 100% uptake) to current participation levels (baseline) and evaluated clinical outcomes and cost for each risk category. The analysis identified low screening uptakes across all family history risk categories (64% in category 1, 62% in category 2, and 56% in category 3). For participants at average risk, 18% reported overscreening; 37% of those in the highest risk categories were screened according to guidelines. With higher screening levels, CRC mortality would be reduced substantially across all risk categories (95 to 305 fewer deaths per 100,000 persons in the 70% scenario versus baseline). For those at average risk, a fully implemented NBCSP represented the most cost-effective approach to prevent CRC deaths (AUS$13,000–16,000 per QALY). For those at moderately increased risk, higher adherence to recommended screening was also highly cost-effective (AUS$19,000–24,000 per QALY).

Comment: CRC is a major contributor to cancer death in the developed world. The benefit of screening using FIT for the prevention and early detection of colon cancer is well known. Unfortunately, rates of uptake of recommended programmes are low for a variety of reasons. A number of groups have investigated the factors contributing to poor uptake and methods to improve it.

Coronado et al. report a study comparing FIT participation rates in patients sent mailed reminders to those receiving usual care. As others have demonstrated, reminders did improve participation, although by a marginal rate. It is interesting to note that implementation rates by participating centres were highly variable, reinforcing the administrative obstacles to programmes such as this.

Brenner et al. compared FIT uptake in patients receiving a mailed reminder or a reminder plus FIT test kit. Rates of completion were approximately 9% higher in the group receiving the kit as well as the reminder, although remained low for both groups. Interestingly, of those who participated and had a positive result, only 67% proceeded to colonoscopy.

These two studies add to the existing evidence that uptake of FIT colon cancer screening is suboptimal, even with reminders. It is not surprising that mailing a FIT kit with reminder letter further improves participation, albeit at a predicted higher cost, with almost 80% of those invited still not participating.

The study reported by Dillon et al. confirms suboptimal uptake of FIT screening in an Australian population. A cost-benefit analysis, although based on some imperfect assumptions, determined that improved adherence to national guidelines as per the Australian NBCSP would result in cost-effective reduction of CRC-related deaths.

Clearly, FIT-based CRC screening is both a clinically and financially effective approach to reducing CRC-related death, however, participation remains suboptimal. It seems that the majority of the population find FIT testing and colonoscopy too unpleasant or inconvenient to consider, regardless of the evidence of benefit in cancer prevention. Further exploration of the barriers to participation from the patient perspective and greater public education and awareness is required to increase community engagement and participation in colon cancer screening.

Reference: PLoS Med. 2018;15(8):e1002630
Abstract

A randomised phase II study of second-line XELIRI regimen versus irinotecan monotherapy in advanced biliary tract cancer patients progressed on gemcitabine and cisplatin

Authors: Zheng Y et al.

Summary: These researchers compared the efficacy and safety of second-line irinotecan alone or in combination with capecitabine (XELIRI regimen) in 64 patients with advanced biliary tract cancer who had progressed after gemcitabine and cisplatin doublet treatment. They were randomised to either single-agent irinotecan 180 mg/m^2 on day 1 of a 14-day cycle or irinotecan 180 mg/m^2 on day 1 plus capecitabine 1000 mg/m^2 twice daily on days 1–10 of a 14-day cycle. Treatments were repeated until disease progression or unacceptable toxicity occurred. Outcomes were evaluable for 60 patients. In the irinotecan monotherapy arm, median PFS was 2.4 months, the 9-month survival rate was 32.0%, median OS was 7.3 months, and the disease control rate was 50.0%; corresponding values in the XELIRI arm were 3.7 months, 60.9%, 10.1 months, and 63.3%, respectively. The most common grade 3 or 4 toxicities were leucopaenia and neutropaenia.

Comment: Biliary tract cancers are often diagnosed at an advanced stage and outcomes tend to be poor. Due to their relative infrequency, few randomised studies exist to guide therapy. CTX combinations with some effect in the first-line setting include gemcitabine/cisplatin, gemcitabine/oxaliplatin, gemcitabine/capecitabine, and gemcitabine/*nab*-paclitaxel. The optimal choice of CTX in the second-line setting is even less clear than in first-line, but some evidence exists for FOLFOX, XELOX, FOLFIRI, XELIRI, capecitabine/cisplatin or 5-FU as a single agent. Choices regarding second-line chemotherapy are often dictated by first-line treatment, drug availability, performance status and organ function.

These authors report improved PFS and OS (by 1.3 months and 2.8 months, respectively) with XELIRI when compared to single-agent irinotecan. These results are intuitive, given what we know about the relative efficacy of these two treatments in CRC. This information does not provide much additional clarity in the choice of second-line CTX for this disease. A comparison of XELIRI to one of the other combinations previously investigated for advanced biliary tract cancer may have been more informative.

Reference: Br J Cancer. 2018;119(3):291-5
Abstract

Managing Cancer and Living Meaningfully (CALM): a randomized controlled trial of a psychological intervention for patients with advanced cancer

Authors: Rodin G et al.

Summary: In this Canadian trial, 305 patients with advanced cancer were randomised to receive either usual care (n=154) or a brief, manualised psychotherapeutic intervention termed Managing Cancer And Living Meaningfully (CALM; n=154), which is intended to treat and prevent depression and end-of-life distress in patients with advanced cancer. Patient Health Questionnaire-9 depression scores were lower (reflecting lower depressive symptom severity) in CALM participants compared with the usual care cohort at both the 3-month (Δ = 1.09; p=0.04; Cohen's d, 0.23) and 6-month assessments (Δ = 1.29; p=0.02; Cohen's d, 0.29). Moreover, a significant treatment effect was observed for preparation for end of life at 6 months that favoured CALM compared with usual care. No adverse effects were reported.

Comment: See below.

Reference: J Clin Oncol. 2018;36(23):2422-32
Abstract

Face-to-face and Internet-based mindfulness-based cognitive therapy compared with treatment as usual in reducing psychological distress in patients with cancer: a multicenter randomized controlled trial

Authors: Compen F et al.

Summary: For those patients with cancer who cannot easily participate in face-to-face mindfulness-based cognitive therapy (MBCT), individual Internet-based MBCT (eMBCT) might be a feasible alternative. This study recruited 245 patients with cancer with psychological distress (all had scores of ≥11 on the Hospital Anxiety and Depression Scale) and randomised them to MBCT (n=77), eMBCT (n=90), or treatment as usual (TAU; n=78). Compared with TAU, patients reported significantly less psychological distress after both MBCT (Cohen's d, 0.45; p<0.001) and eMBCT (Cohen's d, 0.71; p<0.001). Improvement in rates of psychiatric diagnosis favoured both MBCT (33% improvement; p=0.030) and eMBCT (29% improvement; p=0.076) compared with TAU (16%), but were not statistically significant. Both MBCT and eMBCT reduced fear of cancer recurrence and rumination, and improved mental health-related quality of life; they also improved mindfulness skills and increased positive mental health compared with TAU (all p values <0.025). There were no improvements in physical health-related quality of life.

Comment: Aside from the physical symptoms of cancer and its treatment, the accompanying psychological effects have significant impact on quality of life. For those treated with curative intent, the magnitude of the ongoing detrimental effects of depression, anxiety and fear of recurrence have only recently been properly appreciated. For those with advanced disease, psychological distress is a common and serious symptom that can have more significant effects on quality of life than physical symptoms.

Until recently, few interventions designed to treat the psychological effects of cancer were available, and relatively little research had been conducted in this area. Fortunately for current day clinicians, there is growing interest and knowledge in the management of cancer-related distress, and increasing assistance available.

Rodin et al. report a brief psychotherapeutic intervention (CALM) for patients with advanced cancer that results in a reduction in depressive symptoms and death-related distress. Compen et al. explored mindfulness-based cognitive therapy (MBCT), either face-to-face or Internet-based, in patients with either early-stage or advanced cancer. Compared to usual care, both methods resulted in reduced psychological distress, reduced fear of recurrence and improved mental health-related quality of life. The demonstration of benefit from a non-face-to-face, Internet-based approach is an important finding, as in clinical practice it is often the practicalities of accessing psychological interventions that are the greatest barriers.

Reference: J Clin Oncol. 2018;36(23):2413-21
Abstract

A randomised phase 2 trial of *nab*-paclitaxel plus gemcitabine with or without capecitabine and cisplatin in locally advanced or borderline resectable pancreatic adenocarcinoma

Authors: Reni M et al.

Summary: This study enrolled 54 CTX-naïve patients aged between 18 and 75 years with locally advanced or borderline resectable pancreatic adenocarcinoma and randomised them to receive either *nab*-paclitaxel, gemcitabine, cisplatin and oral capecitabine (PAXG arm; n=26) or *nab*-paclitaxel followed by gemcitabine (AG arm; n=28). Resections were performed in around one-third of patients in each study arm (31% in the PAXG arm and 32% in the AG arm). At 1 year, PFS was 58% in the PAXG arm and 39% in the AG arm; at 18 months, OS was 69% and 54%, respectively.

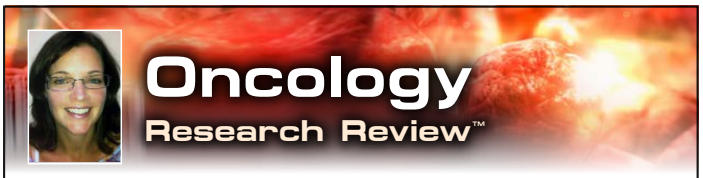
Comment: Pancreatic carcinoma tends to be an aggressive disease with poor outcomes. Even for patients undergoing resection of curative intent, upstaging at the time of surgery and incomplete resection occurs more often than would be predicted by preoperative staging. Consequently, recurrence rates remain high and OS low. There is increasing interest in neoadjuvant CTX for resectable and borderline resectable disease, with the aim of improving resection rates and reducing both local and distant recurrence.

The combination of gemcitabine and *nab*-paclitaxel is effective in the treatment of metastatic pancreatic adenocarcinoma and provides better survival than gemcitabine alone. The more intensive regimen of oxaliplatin, irinotecan and infusional 5-FU (FOLFIRINOX) is also effective in advanced disease, albeit with higher toxicity. The two regimens have not been directly compared.

These authors have conducted a proof-of-principle study exploring the role of preoperative gemcitabine/*nab*-paclitaxel or an intensified regimen of gemcitabine/*nab*-paclitaxel/cisplatin/capecitabine in previously untreated patients with locally advanced/borderline resectable pancreatic carcinoma. In this small group of patients, resection rates exceeded 30% in both groups, with the more intensive regimen providing superior PFS at 12 months and OS at 18 months, without undue additional toxicity.

The selection of chemotherapy regimen in this study is interesting – perhaps gemcitabine/*nab*-paclitaxel versus FOLFIRINOX would have been a more obvious comparison to explore. Nonetheless, the results do support further examination of this approach in larger randomised phase III studies.

Reference: Eur J Cancer. 2018;102:95-102
Abstract



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 carcinoma.

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