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Welcome to the latest issue of Oncology Research Review.

We begin this issue with results from a meta-analysis published in *The BMJ* that assessed the evidence for the benefits and harms of medical cannabis for chronic non-cancer and cancer related pain in adult patients. While the analysis finds moderate to high level certainty evidence for small to very small benefits in pain management, physical functioning and sleep quality, no benefit in emotional or social functioning was found. It should be noted that treatment and follow-up were reasonably short (< six-months) and that longer assessment of therapeutic impacts on emotional functioning might be more accurate, especially given these would not be expected to manifest until after adequate pain control. Three randomised, phase 3 trials – KEYNOTE-590, CheckMate 649 & ESCORT-1st - have demonstrated the clinical benefit of a combined immuno-chemotherapy strategy for first-line treatment of advanced, unresectable esophagogastric carcinomas. The trials assessed different anti- programmed cell death 1 (PD-1) checkpoint inhibitors - pembrolizumab, nivolumab and camrelizumab, respectively – but all found that the combination conferred statistically significant and clinically meaningful survival benefits in all patients, regardless of histology, primary tumour location or PD-ligand (L) 1 expression status. Some differences in the landscape of the ESCORT-1st trial should be noted. Its patient population was entirely Asian and it utilised a different chemotherapy regimen (paclitaxel/platinum compared to fluoropyrimidine/platinum). Based on these results, front-line combination immuno-chemotherapy constitutes a feasible option for the treatment of unresectable esophagogastric cancers. Future work should elucidate optimal patient selection and whether dual checkpoint inhibition elicits further improvements. Finally, a meta-analysis finds evidence to support the otoprotective efficacy of sodium thiosulfate for platinum chemotherapy-induced effects, co-targeting of multiple complementary conformational states of *KIT* may offer a novel therapeutic strategy for refractory gastrointestinal stromal tumours (GIST) and the multitargeted tyrosine kinase inhibitor (TKI) lenvatinib elicits a promising response in patients with advanced previously treated gastroenteropancreatic neuroendocrine tumours in the phase 2 TALENT trial.

We hope you find these and the other selected studies interesting, that they help you improve the lives of your patients and look forward to receiving any feedback you may have.

Kind Regards,

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Abbreviations used in this issue:

CI = confidence interval; **CPS** = combined positive score; **DFS** = disease-free survival; **ECOG** = Eastern Cooperative Oncology Group; **GEP** = gastroenteropancreatic; **GI** = gastrointestinal; **GIST** = gastrointestinal stromal tumours; **GRADE** = Grading of Recommendations Assessment, Development and Evaluation; **GOJ** = gastro-oesophageal junction; **HER2** = human epidermal growth factor receptor 2; **HR** = hazard ratio; **NET** = neuroendocrine tumour; **ORR** = overall response rate; **OS** = overall survival; **pan** = pancreatic; **PD-(L)1** = programmed cell death-(ligand) 1; **PFS** = progression-free survival; **SCC** = squamous cell carcinoma; **TKI** = tyrosine kinase inhibitor.

Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain

Authors: Wang L et al.

Summary: This systematic review and meta-analysis of randomised clinical trials was conducted by a Canadian research group to evaluate the evidence regarding medical cannabis for chronic pain. A search of ten online databases (MEDLINE, EMBASE, AMED, PsycInfo, CENTRAL, CINAHL, PubMed, Web of Science, Cannabis-Med and Epistemonikos) plus trial registries with a cut-off date of January 2021 yielded 32 trials with 5,174 adult patients who have lived with pain for at least three months. Most trials reported results of orally administered (94%) medical cannabis or cannabinoids in comparison to placebo (90%). Three trials had active comparator arms including palmitoylethanolamide, celecoxib, dihydrocodeine, ibuprofen and saw palmetto. Twenty-eight trials enrolled patients with chronic non-cancer pain such as neuropathic, spasticity related, nociplastic, nociceptive or medication overuse headache pain while four trials enrolled patients with cancer-related pain. The median follow-up ranged from one to just over five months. Results of random-effects meta-analyses showed that compared to placebo, non-inhaled medical cannabis elicited a small improvement in pain, physical functioning and sleep quality (assessed as the proportion of patients achieving a ≥ minimally important difference in visual analogue pain scale [VAS], SF-36 scale and 10 cm VAS, respectively, with modelled risk differences of 10%, 4% and 6%). Moderate to high Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty for these improvements were reported. High certainty evidence suggested no benefit in emotional, role or social domains with medical cannabis. Cannabis was associated with a higher risk of transient adverse events including dizziness, cognitive impairment, vomiting, drowsiness, impaired attention and nausea compared to placebo. This article contains a linked clinical practice guideline from a panel of international experts regarding the use of medical cannabis in chronic pain. The guidelines note that recommendations are weak due to the close balance between benefits and harms.

Comment: Chronic pain, either cancer-related or otherwise, has significant effects on quality of life, patient function and healthcare costs throughout the world. There has been a move away from long-term opiate use for non-cancer pain due to troublesome issues of side effects, dependence and overdose. In recent years, there has been growing interest in the potential role for medical cannabis and cannabinoids to treat refractory pain, although data and guidelines are lacking. These authors report a systematic review and meta-analysis of 32 randomised controlled trials of non-inhaled cannabis/cannabinoids in patients with chronic pain. Only four studies related to cancer pain. They used robust data selection and statistical methods to demonstrate that:

1. Compared to placebo, non-inhaled cannabis/cannabinoids may provide a small improvement in pain relief, physical function and sleep quality for a small number of patients with chronic pain.
2. Compared to placebo, non-inhaled cannabis/cannabinoids did not provide measurable improvement in emotional, role or social functioning for patients with chronic pain.
3. Compared to other agents, non-inhaled cannabis/cannabinoids did not provide measurable benefits (accepting small numbers)
4. The use of non-inhaled cannabis/cannabinoids results in a slight increase in transient cognitive impairment, nausea, vomiting and drowsiness and a moderate increase in dizziness in patients with chronic pain.

Data from this meta-analysis was used to create a guideline available at https://www.bmj.com/content/374/bmj.n2040?ijkey=14ccc56559e18685b4ea7bdc2eb02a20634317ec&keytype2=tf_ipsecsha which offers a weak recommendation for a trial of non-inhaled cannabis/cannabinoids in patients with chronic pain despite standard treatment. The existence of such a guideline and supporting evidence is useful, however meaningful discussion with patients regarding the potential advantages and disadvantages of these medications is likely to remain the challenge in clinical practice.

Reference: BMJ 2021;374: n1034
Abstract

Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study

Authors: Sun J-M et al., on behalf of the KEYNOTE-590 Investigators

Summary: First interim analysis results from KEYNOTE-590 (NCT03189719) demonstrate a significant survival advantage to the addition of pembrolizumab to a front-line chemotherapy regimen in advanced esophageal cancer. The global phase 3 Merck Sharp & Dohme Corp. sponsored trial accrued 749 patients with previously untreated, locally advanced or metastatic adenocarcinoma or squamous cell carcinoma (SCC) of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the gastro-oesophageal junction (GOJ), not amenable to curative-intent resection or radiotherapy with measurable disease and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 from 169 medical centres in 26 countries across America, Europe, Australasia and South Africa. Patients received up to 35 cycles of standard of care front-line combination fluoropyrimidine plus platinum-based chemotherapy (5-fluorouracil and cisplatin) ± pembrolizumab. At a median follow-up of almost two-years (22.6 months), pembrolizumab conferred a significant reduction in the risk of death in the entire cohort with a 2.6-month extension in median overall survival (OS; 12.4 vs 9.8 months; hazard ratio [HR] 0.73; 95% confidence interval [CI], 0.62-0.86; $p<0.0001$). Subgroup analysis revealed the survival benefit was most pronounced in patients with PD-L1-positive disease (defined as combined positive score [CPS] ≥10; 13.5 vs 9.4 months; HR 0.62) and in patients with PD-L1-positive SCC disease (13.9 vs 8.8 months; HR 0.57). A significant extension in progression-free survival (PFS) was also reported in the entire population as well as the PD-L1-positive and esophageal SCC subgroups (HRs 0.65, 0.51 and 0.54, respectively). Treatment-related adverse events ≥ grade 3 were reported in 72% of the pembrolizumab/chemotherapy arm and 68% of the standard chemotherapy arm.

Reference: Lancet 2021;398(10302):759-71
Abstract

First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649)

Authors: Janjigian Y et al.

Summary: Data from the randomised, open-label, phase 3 CheckMate 649 (NCT02872116) trial published in *The Lancet* show that the addition of nivolumab to front-line chemotherapy improves both PFS and OS in advanced esophagogastric adenocarcinoma. Patients with previously untreated, advanced/unresectable or metastatic, human epidermal growth factor receptor 2 (HER2)-negative gastric, GOJ or esophageal adenocarcinoma were enrolled from sites around the world and randomised to one of the three treatment arms: nivolumab plus chemotherapy (capecitabine and oxaliplatin [XELOX] every three weeks or leucovorin, fluorouracil, and oxaliplatin [FOLFOX] every two weeks; n=789), nivolumab plus ipilimumab, or chemotherapy alone (n=792). PD-L1 status was not a prerequisite for trial inclusion. Enrolment to the nivolumab/ipilimumab arm was terminated after failing to demonstrate superior survival versus chemotherapy. At a minimum follow-up of one-year (12.1 months), nivolumab plus chemotherapy conferred statistically significant and clinically meaningful OS and PFS benefits among patients with a PD-L1 CPS of ≥ 5 (the dual primary trial endpoints; HR 0.71, 98.4% CI, 0.59-0.86 and HR 0.68, 985 CI 0.56-0.81; both $p<0.0001$). Significant PFS and OS benefits were also reported with nivolumab/chemotherapy in patients with lower PD-L1 expression (CPS ≥ 1) and in the overall cohort.

Reference: Lancet 2021;398(10294):27-40
Abstract

Effect of camrelizumab vs placebo added to chemotherapy on survival and progression-free survival in patients with advanced or metastatic esophageal squamous cell carcinoma

Authors: Luo H et al., for the ESCORT-1st Investigators

Summary: The ESCORT-1st randomized clinical trial (NCT03691090) enrolled patients (n=596; median age 62 years) with previously untreated unresectable locally advanced/recurrent or metastatic esophageal SCC to assess the addition of camrelizumab to front-line chemotherapy. Results at a median follow-up of 10.8 months published in *JAMA* demonstrate that compared to chemotherapy alone (n=298), camrelizumab-chemotherapy (n=298) conferred a significant survival and PFS advantage (OS, 15.3 vs 12 months; HR 0.70; 95% CI, 0.56-0.88; 1-sided $p=0.001$. PFS, 6.9 vs 5.6 months; HR 0.56; 95% CI, 0.46-0.68; 1-sided $p<0.001$) without increasing toxicity (≥ grade 3 treatment-related adverse events, 63.4% vs 67.7%; treatment-related deaths, 3% vs 3.7%).

Reference: JAMA 2021;326(10):916-25
Abstract

Comment: Most cases of oesophageal, GOJ and gastric carcinoma present at an advanced stage, and even with available systemic treatments median survival remains below one year. Platinum-based chemotherapy (plus herceptin for HER2 over-expressing tumours) has been the mainstay of first-line treatment for some time. Despite encouraging results in other tumour types, studies of checkpoint inhibitor monotherapy in advanced esophagogastric carcinoma have been disappointing. Here, we see three positive studies of combined immunotherapy and chemotherapy in patients with advanced esophagogastric carcinoma. The clinical relevance of specific subtypes of esophagogastric carcinoma has long been a source of uncertainty (oesophageal vs GOJ vs gastric; adenocarcinoma vs SCC). As is often the case, each of these three studies varies in patient population with respect to tumour location and histology. Nonetheless, the results of each are encouraging, and when considered in conjunction perhaps even more so. The KEYNOTE-590 study reports clear improvements in OS and PFS for patients with advanced oesophageal or GOJ carcinoma when pembrolizumab was added to cisplatin/ fluorouracil chemotherapy in the first-line setting. The magnitude of benefit was greatest for those with PD-L1 CPS ≥10 SCC (HR 0.57), however benefit was seen in all groups analysed. Whilst there was unequivocal benefit for patients with SCC (HR 0.72), there was also benefit seen in the population overall (HR 0.73), of which 27% had adenocarcinoma. However, the study was not powered to assess for differences related to histology. The CheckMate 649 study also reports OS advantage from the addition of checkpoint inhibition to chemotherapy in the first-line setting, this time using nivolumab with oxaliplatin-based chemotherapy in patients with non-HER2-positive adenocarcinoma from either oesophagus, GOJ or stomach. The magnitude of benefit was greatest in those with PD-L1 CPS ≥5 (HR 0.68), however, benefit was still seen in patients whose tumours had PD-L1 CPS ≥1 (HR 0.77) and in all enrolled patients (HR 0.80). In the small subset of patients with microsatellite unstable tumours, OS benefit was particularly high (HR 0.33). The ESCORT-1st study reports both PFS (HR 0.56) and OS (HR 0.70) benefit from the addition of the checkpoint inhibitor camrelizumab to paclitaxel/cisplatin chemotherapy in the first-line treatment of patients with advanced oesophageal SCC. PD-L1 tumour proportion score greater than 1% was associated with a trend to improved OS, although not statistically significant. Adverse events in all three studies were acceptable and as predicted. Clearly there is a role for the addition of checkpoint inhibition to chemotherapy in the first-line treatment of patients with advanced esophagogastric carcinoma. Whilst detailed information is lacking regarding the interchangeability of the checkpoint inhibitor agents studied, the role of histology and location of primary tumour, and about ideal patient selection methods, these results do represent major progress in the treatment of these tumours, with evidence to support the combined immuno-chemotherapy approach in adeno and squamous histology, and oesophageal, GOJ and gastric primary location. Future studies should focus on assessment of the role of PD-L1 and different testing methods on patient selection and the effect of histology and HER2 status on treatment efficacy.

Association of sodium thiosulfate with risk of ototoxic effects from platinum-based chemotherapy.

Authors: Chen C-H et al.

Summary: This systematic review and meta-analysis from a group in Taiwan investigated the evidence in the literature for the prophylactic efficacy of sodium thiosulfate for reduction of platinum-based chemotherapy induced ototoxic effects. From a search of five online databases up to November 7, 2020 the researchers identified four clinical trials including 278 patients with cancer that reported results for ototoxic effect development such as hearing loss, vertigo and tinnitus with (n=158) versus without (n=133) sodium thiosulfate administration concurrent with platinum-based chemotherapy. Random-effects meta-analysis found a significantly reduced risk of ototoxic effects during platinum-based chemotherapy with the concurrent use of sodium thiosulfate (relative risk 0.61; 95% CI, 0.49-0.77; $p<0.001$; $I^2=5.0\%$). This otoprotective effect appeared to be exerted without a statistically significant compromise in oncologic-related outcomes (event-free survival, HR 1.13; $p=0.61$; $I^2=0\%$. OS; HR 1.90; 95% CI, 0.90-4.03; $p=0.09$; $I^2=0\%$) although the researchers noted that further large-scale studies were required to definitively confirm this.

Comment: Despite recognised significant toxicities, platinum chemotherapy agents remain the mainstay of treatment for several cancer types, including in the curative setting. Whilst advances have been made in the management of platinum-induced nausea, vomiting and nephrotoxicity, progress in the prevention and management of platinum-induced ototoxicity has been slower. It is recognised that platinum can remain in the cochlea indefinitely after treatment, causing sensorineural hearing loss, tinnitus and vestibulopathy. Current practices centre on early identification of ototoxicity and cessation of platinum treatment, rather than prevention of ototoxicity. Sodium thiosulfate has been identified as a potential otoprotective agent, through its ability to protect cells from apoptosis. This agent has also been shown to bind directly to cisplatin in some studies, raising concern for potential reduction of antitumour effects. Transtympanic delivery of the drug has been explored in some studies in an attempt to obtain the otoprotective effects of sodium thiosulfate without adversely affecting treatment outcomes. To date results have been conflicting and inconclusive. These authors report a meta-analysis of four clinical studies of sodium thiosulfate in patients receiving platinum chemotherapy. A total of 278 patients were enrolled in the four studies, which had key differences in design (three were randomised and one non-randomised; three administered sodium thiosulfate intravenously and one via the transtympanic approach; three involved cisplatin and one involved carboplatin therapy). Their results support a protective effect of this agent with significantly reduced ototoxicity (relative risk 0.61). What is less clear is the effect on treatment efficacy. Whilst no significant differences in event-free or overall survival were identified, the small numbers limit the validity of this data. There remains a lack of clarity about the preferred route of administration of this agent, and the effect on anti-cancer treatment outcomes. Further larger randomised studies are required before sodium thiosulfate could be recommended as part of routine care.

Reference: JAMA Netw Open 2021;4(8): e2118895
Abstract

Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study

Authors: Rumgay H et al.

Summary: According to a population-based study from the International Agency for Research on Cancer in collaboration with the World Health Organisation published in *The Lancet Oncology* the global proportion of cancer attributable to alcohol consumption is approximately 4%. The researchers used 2010 alcohol consumption estimates from the Global Information System on Alcohol and Health and applied relative risk estimates from the literature to cancer incidence data from the online Global Cancer Incidence, Mortality and Prevalence database (GLOBOCAN 2020). In 2020, 741,300 new cancer diagnoses worldwide were ascribable to alcohol consumption, a population attributable fraction of 4.1%. More than three-quarters (76.5%) of the population with alcohol attributable cancer were male. The most common types of alcohol related cancer were esophageal (25.6%), liver (20.8%) and breast (13.3%). Almost half (46.7%) of alcohol attributed cancer cases were associated with heavy alcohol consumption, defined as >60g per day, while risky drinking contributed to a further 39.4% of cases. Moderate and light drinkers (<20 g and ≤ 10 g per day, respectively) contributed considerably less burden with 13.9% and 4.8%, respectively. A breakdown of alcohol related cancer risk by region found that the highest proportions of alcohol attributed cancer cases were found in Eastern and Central East Europe (5.7% and 5.6%) while Northern Africa and Western Asia had the lowest proportions (0.3% and 0.7%).

Comment: This is an interesting article that highlights the magnitude of an already appreciated problem. Alcohol has long been recognised as a major contributing factor to many health problems, and is responsible for significant global health cost burden. These authors used cancer incidence data from GLOBOCAN 2020 and alcohol consumption estimates from the Global Information System on Alcohol (2010) to estimate the contribution of alcohol consumption to global cancer incidence in 2020. The data suggests alcohol consumption was responsible for 741,300 cancers in 2020 (4.1% of all cancers), with a predominance of males affected (76.7%) and a predominance of oesophageal, liver and breast cancers. The relationship of alcohol consumption and cancer was linked to the amount of alcohol consumed in a predictable way (heavy>risky>moderate> under 10 g daily). This is obviously an imperfect model based on estimated alcohol intake with an assumed latency of 10 years from intake to cancer diagnosis, however it is a reasonable surrogate for large longitudinal cohort studies which pose their own data analysis challenges. The real challenge is that of encouraging changes in long established and widespread behaviour in the community.

Reference: Lancet Oncol 2021;22(8):1071-80
Abstract

Long-term efficacy of neoadjuvant chemoradiotherapy plus surgery for the treatment of locally advanced esophageal squamous cell carcinoma

Authors: Yang H et al.

Summary: The NEOCRTEC$_{50}$10 (Neoadjuvant Chemoradiotherapy for Esophageal Cancer 5010) randomised clinical trial (NCT01216527) assessed if neoadjuvant chemoradiotherapy conferred a significant survival advantage in patients with resectable locally advanced esophageal SCC. Patients (n=451; median age 56.5 years; 81.4% male) with thoracic esophageal SCC (stage T1-4N1M0/T4N0M0), accrued from centres across China, were randomised to undergo concurrent preoperative vinorelbine/cisplatin chemotherapy and radiotherapy (40 Gy administered in 20 fractions) prior to Mckeown modification surgery and total two-field lymphadenectomy (n=224) or surgery alone (n=227). At a median follow-up of almost five-years (53.5 months) almost half of the patients had died. Analysis of the intention-to-treat population showed an absolute 10% fewer deaths with the addition of neoadjuvant chemoradiotherapy (five-year OS, 59.9% vs 49.1%) and a 26% reduced risk of death (HR 0.74; 95% CI, 0.57-0.97; $p=0.03$). A benefit was also observed in disease-free survival (DFS; 63.6% vs 43%; HR 0.60; 95% CI, 0.45-0.80; $p<0.0001$).

Comment: Even after curative-intent surgical resection, almost three-quarters of patients die from recurrence of their early-stage esophageal carcinoma. Earlier studies have identified a role for adjuvant and/or neoadjuvant treatment to improve outcomes in this group. The results of the CROSS study have resulted in widespread adoption of neoadjuvant chemoradiation for these patients. The authors of this study were interested to clarify the benefit of neoadjuvant chemoradiation for patients with oesophageal SCC, based on the fact that >90% of oesophageal cancers in Asia are of squamous histology and that the CROSS study did not provide information regarding differing outcomes by histology. Results have been previously reported after a minimum 24-month follow-up, demonstrating improvements in both DFS and OS. This paper reports survival results after longer follow-up (minimum five years), and confirms long-term benefit for the use of cisplatin/vinorelbine chemotherapy in conjunction with radiotherapy. It is pleasing to see confirmation of benefit in the subset of patients with oesophageal SCC. The ideal choice of chemotherapy combination in neoadjuvant chemoradiation is unclear due to the use of differing regimens in this and the CROSS study. Until comparative results are available the use of either regimen would be reasonable.

Reference: JAMA Surg 2021;156(8):721-29
Abstract

Association of combination of conformation-specific KIT inhibitors with clinical benefit in patients with refractory gastrointestinal stromal tumours

Authors: Wagner A et al.

Summary: A phase 1b/2a nonrandomised clinical trial (NCT02401815) sponsored by Cogent Biosciences, Inc. in collaboration with the American drug discovery company Plexxikon has reported synergistic activity for simultaneous targeting of two complementary conformational states of *KIT* with a type 1 and a type 2 inhibitor in patients with refractory gastrointestinal stromal tumours (GIST). The US multicentre trial assessed PLX9486 monotherapy (at doses of between 250 – 1000 mg/day) in the dose escalation part of the trial in patients with solid tumours and subsequently in a dose escalation part in combination with either pexidartinib or sunitinib (both inactive-state type 2 inhibitors). This publication in *JAMA Oncology* provides results for the 39 adult patients (median age 57; 56.4% male) with locally advanced, unresectable or metastatic GIST who received PLX9486 ± sunitinib. Most (89.7%) had treatment-refractory disease with the rest progressive disease following standard therapy. The recommended phase 2 dose of PLX9486 was determined to be 1000 mg/day. Sunitinib was administered at doses of either 25 or 37.5 mg/day. Longer median PFS and higher clinical benefit rates were found with the combination therapy compared to PLX9486 monotherapy (PFS, 12.1 vs 5.75 months. Clinical benefit rate, 80% vs 50%). The authors concluded that this strategy showed promising anti-tumour activity in patients with refractory GIST.

Comment: Most GISTs are driven by primary activating mutations in exons 9 or 11 of the *KIT* gene. These mutations are effectively targeted by the tyrosine kinase inhibitor (TKI), imatinib. Despite initial response to this agent, resistance invariably occurs due to growth of inherently resistant clones or the acquisition of secondary resistance mutations affecting exons coding for either the ATP binding pocket (13 or 14) or activation loop (17 or 18) of the *KIT* gene. The accepted second- and third-line treatment options for GIST at the time of inception of this study included sunitinib and regorafenib. The clinical utility of these agents is limited by the fact that they are only effective against some of the known secondary resistance mutations (sunitinib vs ATP binding pocket mutations, regorafenib vs some activation loop mutations). More recently, ripretinib a novel switch-pocket inhibitor has been shown to have a role in multi-resistant metastatic GIST. These researchers used x-ray crystallography to explore the molecular mechanism of resistance of GIST tumours to standard TKIs, and identified a conformational change in the *KIT* gene which renders standard TKIs unable to bind to the gene. Using this information they developed a new agent, PLX9486 which is specifically designed to be able to bind in the presence of the identified conformational change. This paper reports results of the phase 1b-2a study of this agent, nominating the preferred dose as 1000 mg/day in combination with sunitinib, enabling deliberate targeting of multiple known mutations implicated in GIST. Results are supportive of this approach with the combination resulting in increases in PFS and clinical benefit. The logical and targeted scientific approach described in this paper is pleasing. Larger randomised studies of the combination are awaited with interest.

Reference: JAMA Oncol 2021;7(9):1343-50
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.

Lenvatinib in patients with advanced grade 1/2 pancreatic and gastrointestinal neuroendocrine tumours

Authors: Capdevila J et al.

Summary: Results of the phase 2 TALENT trial (GETNE1509) indicate that lenvatinib may be a therapeutic option for advanced previously treated gastroenteropancreatic neuroendocrine tumours (GEP-NETs). The single-arm, open-label trial accrued patients (n=111) with advanced/metastatic histologically confirmed, grade 1/2 neuroendocrine tumours of the pancreas (panNET; n=55) or gastrointestinal tract (GI-NET; n=56) from centres in Austria, Italy, Spain and the UK. Patients in the panNET cohort had radiologically confirmed progressive disease following ≤ one line of target agent therapy such as a mTOR inhibitor or antiangiogenic agent. Patients in the GI-NET cohort had disease originating from the stomach, small intestine or colorectal that progressed after somatostatin analogues therapy such as octreotide or lanreotide and/or interferon treatment. At an almost two-year median follow-up (23 months), the overall response rate (ORR) was 29.9%, with the panNET cohort achieving an ORR of 44.2% and the GI-NET cohort 16.4%. Median duration of response was 19.9 and 33.9 months in the cohorts, respectively. The median PFS was 15.7 months.

Comment: Systemic therapies for the treatment of grade 1 – 2 metastatic GEP-NETs are limited in number and effect. Somatostatin analogues have a definite role in the management of symptoms related to hormone secretion, and a probable role in disease control, although they have not demonstrated conclusive reduction in tumour burden in clinical studies to date. On the other hand, peptide receptor radionuclide therapy can definitely lead to reduced tumour burden in appropriately selected patients, however its utility can be limited by disease distribution. Targeted TKIs have a role in the treatment of pan-NETs, but as yet have not shown clear benefit in the treatment of GI-NETs. Expanded treatment options are needed. Based on the understanding that GEP-NETs express high levels of angiogenic molecules, these investigators conducted a single-arm phase 2 study of lenvatinib, a multitargeted antiangiogenic TKI, in previously treated GEP-NETs. Their results suggest that lenvatinib warrants further study in this context, with an ORR of 29.9% and PFS of 15.7 months. The explanation for the differences in response rates and duration of response between pan-NETs and GI-NETs is not immediately clear, with responses in pan-NETs reportedly of greater magnitude but less durability than those in GI-NETs. Future randomised studies should focus on further elucidating the differences in response rates, durability of response and clinical benefit in these two subgroups of NET.

Reference: J Clin Oncol 2021;39(20):2304-12
Abstract

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Early weight loss as a prognostic factor in patients with advanced gastric cancer

Authors: Mansoor W et al.

Summary: Analyses from REGARD, RAINBOW, and RAINFALL phase 3 studies reveal that weight-loss of ≥ 3% during the first cycle of systemic therapy is a negative prognostic factor for survival in patients with locally advanced or metastatic gastric or GOJ adenocarcinoma. Post hoc analysis was conducted of 1,464 patients enrolled in the trials (REGARD, n=311; RAINBOW, n=591 and RAINFALL, n=562) who received first- or second-line standard chemotherapy or best supportive care ± ramucirumab. A less than 3% weight-loss, compared to ≥ 3% weight loss, in the first three to four weeks of systemic therapy was associated with longer survival and a statistically significant reduced risk of death in each trial (REGARD, 5.8 vs 2.6 months, HR 0.36; RAINBOW, 9.8 vs 7.3 months, HR 0.63; RAINFALL, 11.7 vs 9.7 months, HR 0.75). This association remained significant on pooled analysis, after adjustment for confounding factors such as ECOG performance status and peritoneal metastasis, and regardless of trial arm (pooled analysis; ramucirumab arms, HR 0.69, placebo arms, HR 0.56).

Comment: The prognostic significance of weight loss in patients with advanced gastric cancer has been previously established, with a clear link between loss of ≥10% of weight and poorer outcomes. The causes of weight loss in these patients are multifactorial and include anorexia, dysphagia, enforced fasting for medical interventions and disease-related cachexia. These authors report a post hoc analysis of data from three studies of ramucirumab in advanced gastric cancer, exploring the relationship between 'minimal early weight loss' (loss of ≥3% weight during the first cycle of chemotherapy) and survival. Unsurprisingly, they report 'minimal early weight loss' as a negative prognostic factor in these patients. It is difficult to see what this data adds to conventional wisdom. Given its post hoc nature the validity can be called to question. Validity aside, the assessment of the prognostic impact of arbitrarily assigned quantities of weight loss over discreet periods of time is not clinically useful. Exploration of approaches to reduce weight loss in this population, and the effects of those approaches on survival would be far more useful to clinicians.

Reference: Oncologist 2021;26(9): e1538-47
Abstract

