Oncology Research Review™

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In this issue:

Abbreviations used in this issue:

CLM = colorectal liver metastases; **CRC** = colorectal cancer; **CT** = computed tomography; **DFS** = disease-free survival; **NSCLC** = non-small cell lung cancer; **OS** = overall survival; **PFS** = progression-free survival; **RT** = radiation therapy; **RTK** = receptor tyrosine kinase; **TKI** = tyrosine kinase inhibitor; **TNI** = tumour-normal interface

Welcome to the fifteenth issue of Oncology Research Review.

Results from the North Central Cancer Treatment Group adjuvant trial N9831 report that a high baseline level of soluble human epidermal growth factor receptor 2 (sHER2) was a prognostic indicator of shorter disease-free survival among patients with early-stage HER2-positive breast cancer. In addition, high levels of the biomarkers at recurrence were found to be predictive of shorter survival. These results suggest interesting possibilities for serial monitoring of tumour response to therapy.

I hope you enjoy this edition and I welcome your comments and feedback.

Kind Regards,

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Multicenter validation study of pathologic response and tumor thickness at the tumor-normal liver interface as independent predictors of disease-free survival after preoperative chemotherapy and surgery for colorectal liver metastases

Authors: Brouquet A et al

Summary: This study included 171 patients who underwent resection of colorectal liver metastases (CLM) after preoperative chemotherapy. The study aim was to validate pathologic markers of response to preoperative chemotherapy as predictors of disease-free survival (DFS). Pathologic response was defined as the proportion of tumour cells remaining (complete, 0%; major, <50%; minor, ≥50%) and tumour thickness at the tumour-normal liver interface (TNI) (<0.5 mm, 0.5 to <5 mm, ≥5 mm). Complete, major and minor pathologic response was achieved by 8%, 49% and 43% of patients, respectively. Tumour thickness at the TNI was <0.5 mm in 21% of patients, 0.5 to <5 mm in 56% of patients, and ≥5 mm in 23% of patients. In multivariate analyses using either pathologic response or tumour thickness at TNI, the following factors were significantly associated with DFS: pathologic response, tumour thickness at TNI, duration of preoperative chemotherapy, number of CLM, and margin. When both parameters were included in multivariate analysis, tumour thickness at TNI, duration of preoperative chemotherapy, number of nodules and margin were all significantly associated with DFS. Tumour size by pathology examination predicted pathologic response. Tumour size and chemotherapy regimen predicted tumour thickness at the TNI.

Comment: At least 50% of patients with colorectal carcinoma (CRC) develop liver metastases at some stage. In the vast majority of these patients their malignancy is incurable. In a small proportion with liver-only disease, however, hepatic resection can be performed with improved 5-year survival outcomes. This approach can result in cure in approximately 30% of such patients. Hepatic resection is usually accompanied by pre- and/or postoperative systemic chemotherapy, although the preferred choice and timing of chemotherapy remains unclear. A previous single-centre study has identified both pathologic response (the proportion of residual viable tumour cells) and tumour thickness at the TNI as factors associated with survival after neoadjuvant chemotherapy and resection of CLM. The purpose of the current study was to validate those measures in a wider patient cohort. Their results support a prognostic role for both pathologic response and tumour thickness in this setting. Of interest is the observation that duration of preoperative chemotherapy exceeding 3 months was associated with poorer 3- and 5-year survival. Also of interest is the finding that treatment with oxaliplatin and bevacizumab was associated with thinner tumour at the TNI. These observations raise questions regarding the optimal regimen and duration of preoperative treatment.

As the authors discuss, further studies using pathologic response and tumour thickness criteria to assess response to preoperative treatment and guide postoperative treatment would be of interest.

Reference: Cancer 2013;119(15):2778-88

http://onlinelibrary.wiley.com/doi/10.1002/cncr.28097/abstract

A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer

Authors: Kim EJ et al

Summary: Preoperative therapy with full-dose gemcitabine, oxaliplatin, and radiation therapy (RT) was evaluated in localised pancreatic cancer. Treatment comprised two 28-day cycles of gemcitabine (1 g/m^2 over 30 minutes on days 1, 8, and 15) and oxaliplatin (85 mg/m^2 on days 1 and 15) with RT during cycle 1 (30 Gray [Gy] in 2-Gy fractions). Patients were evaluated for surgery after cycle 2. Those who underwent resection received 2 cycles of adjuvant chemotherapy. 23 patients had resectable disease, 39 patients had borderline resectable disease, and 6 patients had unresectable disease. Sixty-six patients completed cycle 1 with RT, and 61 patients completed cycle 2. Grade ≥3 adverse events during preoperative therapy included neutropenia (32%), thrombocytopenia (25%), and biliary obstruction/cholangitis (14%). Forty-three patients underwent resection (63%), 36 (84%) of whom achieved complete (R0) resection. The median overall survival (OS) was 18.2 months for all patients, 27.1 months for the resected cohort, and 10.9 months for those who did not undergo resection. A decrease in CA 19-9 level after neoadjuvant therapy was associated with R0 resection (p=0.02), which resulted in a median survival of 34.6 months. At a median 31.4 months' follow-up, 14 patients (21%) remained alive and disease-free.

Comment: Outcomes from pancreatic carcinoma remain disappointing, due to a variety of factors. Most cases present in either locally advanced or metastatic state precluding potentially curable resection. In addition, both local and distant recurrences after resection are common.

These authors investigate the utility of preoperative combined modality treatment with systemic doses of both gemcitabine and oxaliplatin, as well as local radiation. The rationale for using systemic treatment up-front is sound and the combination appeared to be reasonably well tolerated with no increase in surgical complication rate or mortality. Rates of R0 resection were high but median OS remained disappointing (although significantly improved in those undergoing resection when compared to those not). Unfortunately, the primary endpoint of improved 2-year DFS was not met, possibly due to a high number of borderline and unresectable cases. A phase III study in a larger patient cohort is required to truly understand the role for this treatment approach. However, as the authors discuss in some detail, accurate staging and determination of resectability of pancreatic carcinomas remains a major limitation to studies such as these. The application of this information in clinical practice will also be hindered by staging difficulties.

Reference: Cancer 2013;119(15):2692-700
http://onlinelibrary.wiley.com/doi/10.1002/cncr.28117/abstract

Pemetrexed versus erlotinib in pre-treated patients with advanced non-small cell lung cancer: A Hellenic Oncology Research Group (HORG) randomized phase 3 study

Authors: Karampeazis A et al

Summary: Patients with stage IIIB/IV non-small cell lung cancer (NSCLC) who progressed after first- or second-line treatment were randomised to receive either pemetrexed or erlotinib. Squamous cell histology was identified in 21.7% of patients in the pemetrexed arm and 23.5% of patients in the erlotinib arm, and treatment was third-line in 39.2% and 46.4% of patients, respectively. No between-group differences were observed for time to tumour progression (TTP), the objective response rate, or OS. In patients who had squamous cell histology, TTP was prolonged with erlotinib compared with pemetrexed (4.1 months vs 2.5 months, respectively; p=0.006). Pemetrexed was associated with a significantly higher incidence of grade 3 and 4 neutropenia, thrombocytopenia, and asthenia, whereas erlotinib was associated with a higher incidence of grade 3 and 4 skin rash.

Comment: Both pemetrexed and erlotinib have been associated with benefit in pre-treated patients with advanced NSCLC. The activity of pemetrexed is limited in squamous histology NSCLC, and erlotinib is most active in never-smokers or those with *EGFR* mutation. These authors compared outcomes between these two agents in unselected pre-treated NSCLC. Their results suggest equivalence of pemetrexed and erlotinib in the 2nd- or 3rd-line treatment of unselected NSCLC with respect to TTP, progression-free survival (PFS), OS and overall response rate. Unfortunately, several factors make interpretation of these results difficult, including the relatively high proportion of squamous NSCLC that would be expected to do poorly with pemetrexed treatment (excluded from enrolment after July 2008) and small patient numbers. In addition, limited molecular information was available. In subgroup analyses of small patient numbers, those with wt EGFR had better outcomes with pemetrexed than erlotinib, and those with EGFR mutation fared better with erlotinib than pemetrexed. However as mutation status was known in only about one-third of patients, no differences in outcome were seen in the group as a whole. It is difficult to draw firm conclusions from these results.

Reference: Cancer 2013;119(15):2754-64
http://onlinelibrary.wiley.com/doi/10.1002/cncr.28132/abstract

Soluble human epidermal growth factor receptor 2 (HER2) levels in patients with HER2-positive breast cancer receiving chemotherapy with or without trastuzumab: Results from North Central Cancer Treatment Group adjuvant trial N9831

Authors: Moreno-Aspitia A et al

Summary: This study assessed levels of soluble human epidermal growth factor receptor 2 (sHER2) during treatment and at the time of recurrence in patients with early-stage HER2-positive breast cancer who were randomised to treatment arms A (standard chemotherapy), B (standard chemotherapy with sequential trastuzumab), and C (standard chemotherapy with concurrent trastuzumab). Baseline samples were available from 2318 patients, serial samples from 105 patients, and recurrence samples from 124 patients. Within all treatment groups, baseline sHER2 levels ≥15 ng/mL were associated with worse DFS than baseline sHER2 levels <15 ng/mL (arm A: HR 1.81; p=0.0014; arm B: HR 2.08; p=0.0015; arm C: HR 1.96; p=0.01). Among the 124 patients who experienced disease recurrence, sHER2 levels increased from baseline to the time of recurrence in arms A and B but remained unchanged in arm C. High sHER2 levels (≥15 ng/mL) at recurrence were associated with a shorter survival (3-year OS of 51% vs 77% with recurrence sHER2 levels <15 ng/mL; HR 2.36; p=0.01).

Comment: The presence of Her2 receptor amplification has recognised implications on breast cancer prognosis and treatment. Soluble HER2 (sHER2) is the cleaved extracellular domain of the Her2 receptor and can be measured in blood. Higher levels of soluble sHER2 in metastatic breast cancer have been linked with poorer prognosis. However, there remains no consensus as to the clinical utility of this measurement in either metastatic or early-stage breast cancer. These authors describe the pattern of sHER2 levels in women undergoing adjuvant treatment and follow-up for early-stage breast cancer on the N9831 clinical trial (chemotherapy alone vs. chemotherapy and sequential trastuzumab vs. chemotherapy and concurrent trastuzumab). Unfortunately, despite over 2000 patients being enrolled in the clinical trial, the number of serial sHER2 samples available was significantly lower. Their results suggest a prognostic role for sHER2 both at baseline and at recurrence, with high levels at baseline predicting poorer DFS and high levels at recurrence predicting poorer overall survival. This data is interesting and further prospective analyses of sHER2 in prognosis and treatment selection should be undertaken.

Reference: Cancer 2013;119(15):2675-82
http://onlinelibrary.wiley.com/doi/10.1002/cncr.28130/abstract

Matched-pair and propensity score comparisons of outcomes of patients with clinical stage I non–small cell lung cancer treated with resection or stereotactic radiosurgery

Authors: Varlotto J et al

Summary: Outcomes were retrospectively analysed for patients with clinical stage I NSCLC treated between 1999 and 2008 by lobectomy (LR, n=132), sublobar resection (SLR, n=48), or stereotactic body radiotherapy (SBRT, n=137) after negative staging. Median follow-up for all patients was 25.8 months. On univariate analysis, OS was significantly worse with SBRT and also correlated with histology, the Charlson comorbidity index, tumour size, and aspirin use; total recurrence control (TRC; i.e., local-regional and distant control) correlated only with histology; no variable correlated significantly with locoregional control (LRC). In a matched-pair analysis comparing surgery and SBRT results, OS was significantly poorer for SBRT than for patients treated with surgery, but TRC and LRC were not significantly different between these groups. In multivariate analyses including propensity score as a covariate (controlling for all factors affecting treatment selection), OS correlated only with Charlson comorbidity index and TRC correlated only with tumour grade. LRC correlated only with tumour size with or without propensity score correction.

Comment: It is well recognised that anatomical resection results in improved survival when compared to non-anatomical resection of early-stage primary NSCLC. Stereotactic radiosurgery (SRS) or stereotactic ablative body radiotherapy (SABR) involves the delivery of high radiation doses to restricted volumes and has demonstrated promising local control rates in primary NSCLC. Accurate comparison of the outcomes of surgery vs. SRS is made difficult by differences in patient factors affecting treatment selection. It is usually patients with co-morbidities or poor performance status that undergo treatment with SRS rather than surgery and outcomes of this group would be expected to be inferior to those fitter patients undergoing surgical resection. These authors performed a retrospective analysis of treatment outcomes from 4 separate institutions comparing surgical resection to SRS. Unadjusted data demonstrated inferior outcomes in those patients undergoing SRS. However, after adjusting for selection bias using propensity scores there were no differences in OS, local or distant control between groups. This data is obviously limited by its retrospective nature, but does allow us to feel that randomised studies comparing SRS and surgery in these patients is ethical to undertake. Two such studies are under way, with results not expected until at least 2017.

Reference: Cancer 2013;119(15):2683-91
http://onlinelibrary.wiley.com/doi/10.1002/cncr.28100/abstract

USP8 is a novel target for overcoming gefitinib resistance in lung cancer

Authors: Byun S et al

Summary: This paper describes how knockdown of ubiquitin-specific peptidase 8 (USP8) selectively kills gefitinib-resistant NSCLCs with little effect on normal cells. Genetic silencing of USP8 led to the downregulation of several receptor tyrosine kinases (RTKs) including *EGFR*, *ERBB2*, *ERBB3*, and *MET*. Administration of a synthetic USP8 inhibitor markedly decreased the viability of gefitinib-resistant and -sensitive NSCLC cells by decreasing RTK expression, without affecting normal cells. In a mouse xenograft model using gefitinib-resistant and -sensitive NSCLC cells, treatment with a USP8 inhibitor significantly reduced tumour size.

Comment: The development of EGFR tyrosine kinase inhibitors (TKIs) has dramatically altered treatment and outcomes for patients with *EGFR*-mutated NSCLC. Despite initial response, however, the majority of patients treated with these agents develop resistance either through secondary *EGFR* mutation or *MEK* amplification. A variety of approaches to overcome this resistance are under investigation, including the development of novel irreversible EGFR TKIs, combined *EGFR* and *MEK* inhibition and blockade of downstream pathways. USPs are a subgroup of de-ubiquitinating enzymes with roles in deconjugating specific proteins that would otherwise undergo degradation. USP8 is involved in *EGFR* regulation and these authors have demonstrated in preclinical models that USP8 inhibition leads to attenuation of several tyrosine kinase receptors including *EGFR*, *ERBB1*, *ERBB3* and *MET*, with subsequent reduced viability of NSCLC cell lines (both gefitinib-sensitive and -resistant). The effects of this approach appear most dramatic in gefitinib-resistant tumours. They also report an apparent absence of effect on normal cells, postulating that it is only those cells that have become dependent on (or addicted to) RTK pathways that will be affected. Whilst clinical studies are obviously required to determine the tolerability, safety and efficacy of USP8 as a cancer treatment, the potential to simultaneously down-regulate multiple RTKs implicated in gefitinib-resistant NSCLC is very appealing.

Reference: Clin Cancer Res 2013;19(14):3894-904
http://clincancerres.aacrjournals.org/content/19/14/3894.abstract

Modern multidisciplinary treatment of rectal cancer based on staging with magnetic resonance imaging leads to excellent local control, but distant control remains a challenge

Authors: Engelen SM et al

Summary: This study evaluated whether a differentiated treatment of primary rectal cancer based on magnetic resonance imaging (MRI) can reduce the number of incomplete resections and local recurrences and improve recurrence-free and overall survival. The study recruited 296 patients with rectal cancer who underwent preoperative MRI using a lymph node-specific contrast agent to predict circumferential resection margin (CRM), T- and N-stage. Patients were stratified according to MRI results: (a) low risk for local recurrence (CRM >2mm and N0 status), (b) intermediate risk and (c) high risk (close/involved CRM, N2 status or distal tumours). Mainly based on this MRI risk assessment patients were treated with (a) surgery only (TME or local excision), (b) preoperative 5 × 5 Gy+total mesorectal excision (TME) and (c) a long course of chemoradiation therapy followed by surgery after 6 to 8 weeks. A total of 228 patients underwent treatment with curative intent: 49 with surgery only, 86 with 5 × 5 Gy and TME and 93 with chemoradiation and surgery. The number of complete resections (margin >1mm) was 218 (95.6%). At a median 41-month follow-up, the 3-year local recurrence rate, DFS rate and OS rate was 2.2%, 80% and 84.5%, respectively.

Comment: Optimal local treatment of non-metastatic rectal carcinoma depends on the local disease stage, with stage I tumours (T1-2, N0) being appropriately treated with surgery alone (TME), and more locally advanced tumours requiring either short-course preoperative radiotherapy or long-course combined chemoradiation. MRI has proven to be the best available method of determining pre-treatment tumour stage. The aim of this study was to document outcomes of rectal cancer treatment using a predefined treatment algorithm based on MRI staging. The authors report a high proportion of complete resections and good local control, with results comparing favourably to historical controls. They believe their results support the use of a defined treatment algorithm for early rectal carcinoma in the context of multidisciplinary case review, although they do acknowledge that these findings are non-randomised. Postoperative mortality was 4% and post-treatment function and quality of life were not reported. It is possible that some patients are over-treated using this approach, however, MRI-guided local treatment remains the preferred approach for these patients at present. In addition to local control, prevention of systemic metastasis is necessary and will have the greatest impact on overall survival.

Reference: Eur J Cancer 2013;49(10):2311-20
http://www.ejcancer.com/article/S0959-8049(13)00192-5/abstract

Expectations about the effectiveness of radiation therapy among patients with incurable lung cancer

Authors: Chen AB et al

Summary: This research group from the Dana-Farber Cancer Institute investigated patient expectations about the goals of RT for incurable lung cancers. The study included 384 patients diagnosed with stage wet IIIB or IV lung cancer given RT. Seventy-eight percent believed that RT was very or somewhat likely to help them live longer, and 67% believed that RT was very or somewhat likely to help them with problems related to their cancer. However, 64% did not understand that RT was not at all likely to cure them. Older patients and nonwhites were more likely to have inaccurate beliefs, and patients whose surveys were completed by surrogates were less likely to have inaccurate beliefs. Ninety-two percent of patients with inaccurate beliefs about cure from RT also had inaccurate beliefs about chemotherapy.

Comment: Lung cancer remains the leading cause of cancer death in developed countries. Palliative treatments are available and can improve outcomes, however, there is good evidence to show that cancer patients often have unrealistic expectations about their prognosis and the potential utility of treatment. In addition, there is evidence to suggest that treating doctors may be overly optimistic about the benefits of treatment, and have difficulty communicating details of prognosis to patients.

It is important for patients to understand the potential benefits and limitations of treatment to enable them to make informed treatment decisions. This group has previously shown that a significant proportion of advanced lung and colon cancer patients undergoing chemotherapy did not understand that their treatment had no possibility of providing cure. The results of the current study are strikingly similar, with 64% of patients failing to understand that radiotherapy was not a curative treatment in their case.

The factors leading to such misunderstandings are complex. It appears there may be cultural and generational differences in the beliefs of patients about cancer and cancer treatment. Certainly, the opinion of the treating doctor and the efficacy of communication regarding these factors also play a role. What is not clear from this study is whether patients had never been accurately informed about their prognosis and the aims of treatment, whether they had misunderstood information, or whether they refused to believe it. It will be important to understand where the main barriers in communication exist in order to design effective interventions.

Reference: J Clin Oncol 2013;31(21):2730-5
http://jco.ascopubs.org/content/31/21/2730.abstract

Targeting of low-dose CT screening according to the risk of lung-cancer death

Authors: Kovalchik SA et al

Summary: Data were analysed from the National Lung Screening Trial (NLST) to assess the association between lung cancer risk and the benefit of screening in 26,604 trial participants who underwent low-dose CT screening and 26,554 participants who underwent chest radiography. The 5-year risk of lung cancer death ranged from 0.15 to 0.55% in the lowest-risk group (quintile 1) to >2.00% in the highest-risk group (quintile 5). The number of lung cancer deaths per 10,000 person-years that were prevented in the CT-screening group, compared with the radiography group, showed a significant increasing trend according to risk quintile (0.2, 3.5, 5.1, 11.0, and 12.0 across quintiles 1 through 5, respectively). Across risk quintiles, there were significant decreasing trends in the number of participants with false positive results per screening-prevented lung cancer death (1648, 181, 147, 64, and 65 across quintiles 1 through 5, respectively). Among the 60% of participants who were at the highest risk for lung cancer death (quintiles 3 through 5), 88% of the screening-prevented lung cancer deaths and 64% of the false-positive results occurred. The 20% of participants at lowest risk (quintile 1) accounted for only 1% of prevented lung cancer deaths.

Comment: The recent NLST demonstrated a 20% reduction in the risk of lung cancer mortality with the use of low-dose CT screening when compared to plain X-ray in a selected patient group. These results have strengthened the argument for lung cancer screening in at-risk populations, however, a lack of clarity regarding how best to define the high-risk population persists. These authors have further analysed the data from the NLST to demonstrate that the benefits of low-dose CT screening vary with pre-screening risk. Factors used to categorise risk included age, BMI, family history of lung cancer, pack-year smoking history, years since smoking cessation and diagnosis of emphysema.

The demonstration of a lower number needed to screen and reduced false-positive rate in those at highest risk of lung cancer death supports the use of such a risk assessment tool in selecting patients for screening. This has major public health implications.

Reference: N Engl J Med 2013;369(3):245-54
http://www.nejm.org/doi/full/10.1056/NEJMoa1301851

Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial

Authors: Wu YL et al

Summary: The FASTACT-2 trial randomised 451 patients with untreated stage IIIB/IV NSCLC to 6 cycles of gemcitabine (1250 mg/m^2 on days 1 and 8, intravenously) plus platinum (carboplatin 5 × area under the curve or cisplatin 75 mg/m^2 on day 1, intravenously) with intercalated erlotinib (150 mg/day on days 15–28, orally; n=226) or chemotherapy plus oral placebo (n=225), every 4 weeks. Treatment continued until progression or unacceptable toxicity or death, and all patients in the placebo group were offered second-line erlotinib at the time of progression. PFS was significantly prolonged with chemotherapy plus erlotinib versus chemotherapy plus placebo (median PFS 7.6 months vs 6.0 months; HR 0.57; p<0.0001); median OS values were 18.3 months and 15.2 months, respectively (HR 0.79; p=0.0420). Treatment benefit was noted only in patients with an activating *EGFR* gene mutation (median PFS 16.8 months vs 6.9 months; HR 0.25; p<0.0001; median OS 31.4 months vs 20.6 months; HR 0.48; p=0.0092). Serious adverse events were reported by 34% of patients in the chemotherapy plus placebo group and 31% of the chemotherapy plus erlotinib group. The most common grade ≥3 adverse events were neutropenia (29% and 25% of patients, respectively), thrombocytopenia (14% in each arm), and anaemia (12% and 9%, respectively).

Comment: In patients with *EGFR*-mutated advanced NSCLC, the use of EGFR TKIs is the preferred first-line treatment option. Earlier studies combining EGFR TKIs with cytotoxic chemotherapy failed to show benefit, possibly due to TKI-induced G1 cell cycle arrest inhibiting the effect of chemotherapy. The phase II FASTACT study demonstrated improved outcomes in a molecularly unselected Asian NSCLC population by using sequential intercalated erlotinib and chemotherapy. The results of this (drug company-sponsored) confirmatory phase III study also show benefit although that benefit is confined to those with *EGFR* mutation. But is intercalated therapy better than, or even as good as, EGFR TKI therapy alone in patients with *EGFR*-mutated advanced NSCLC? This needs confirmation in randomised studies with EGFR TKI monotherapy as the control arm.

Reference: Lancet Oncol 2013;14(8):777-86
http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(13)70254-7/abstract