Journal Reviews

Clinical Breast Cancer

Prognostic clinico-pathological factors on multivariate analysis following preoperative systemic chemotherapy for triple negative breast cancers

Asaga S, Kinoshita T, Hojo T, Suzuki J, Jimbo K, Tsuda H. Clinical Breast Cancer 2013 Feb;13(1):40-6.

This is a retrospective follow up study aimed to identify significant prognostic factors for triple negative breast cancer (TNBC) patients receiving preoperative systemic chemotherapy (PST). A total of 135 triple negative breast cancer patients amongst the 4195 operable primary breast cancer patients were analysed for significant prognostic factors among different clinical and pathological variables. Kaplan-Meier curves and Cox proportional hazard modelling statistical tests were used in a univariate and multivariate analysis for disease-free survival (DFS) and overall survival (OS). Among the 135 triple-negative breast cancer patients, the median patient age was recorded at 54 years, median tumour diameter on palpation was found to be 4.5 cm, and there were 62 patients who had clinically node positive disease. Following anthracycline-taxane (Epirubicin, Doxorubicin, Cyclophosphamide and Paclitaxel) chemotherapy in concurrent (up to 2002), sequential and isolation regimens; the clinical response and pathologic complete response rates recorded was 76% (103 patients) and 21% (29 patients) respectively. Median disease-free survival was found to be 44.4 months and median overall survival 49.2 months. Univariate and multivariate analysis showed that that completion of chemotherapy, better clinical response, fewer positive nodes, and lower histologic grades were significant factors associated with both disease-free and overall survival.

Reviewer's opinion: This is a small retrospective study aimed at analysing other clinico-pathological factors (besides the pathological complete response; pCR) as prognostic markers in TNBC subtype following preoperative systemic chemotherapy in Japanese population. Previous studies have shown pCR following PST as an independent prognostic marker across all breast cancer subtype including TNBC. However, it is well known that TNBC subtype tends to develop visceral metastasis and show aggressive phenotype despite high pCR rates. This study therefore, assessed other clinico-pathological variables such as completion of PST, clinical response, T and N status, lymphatic and vascular invasion, and histological grade alongside pCR for DFS and OS in a multivariate analysis. Interestingly the findings from this study showed completion of PST and clinical response and not pCR as strong surrogate markers of favourable prognosis. Further, TNBC patients with a family history of breast cancer were found to have similar prognosis to patients with sporadic disease with the phenotype. This study is first to assess the role of pCR as independent prognostic marker with anthracycline-taxane primary systemic chemotherapy focused on TNBC subtype. The study findings challenge the status of pCR as independent prognostic factor the TNBC subtype; it provides researchers a much food for thought to consider the role of clinical response as a prognostic marker in the TNBC phenotype in larger studies. – TH

Alteration of HER2/neu status following neoadjuvant chemotherapy in invasive breast cancer

Influence of neoadjuvant chemotherapy on HER2/neu status in invasive breast cancer. Li P, Liu T, Wang Y, Shao S, Zhang W, Lv Y, Yi J, Wang Z. Clinical Breast Cancer 2013 Feb;13(1):53-60.

The study evaluates HER2/neu status of invasive breast cancers on core biopsies and surgical resections following neoadjuvant chemotherapy treatments (NACT). Reliably estimating HER2/neu expression in breast cancer is important for predicting patient prognosis and optimising adjuvant therapeutic strategies. A total of 131 patients with primary breast cancer treated with anthracycline-and/or taxane-based NACT were evaluated by immunohistochemical (IHC) study for HER2/neu status on core needle biopsies before NACT and residual breast cancers surgical resection specimens or-positive axillary lymph nodes post-NACT. Thirty-two pairs of specimens with discordant HER2/neu IHC scores were analysed by fluorescence in situ hybridisation (FISH). After NAC, 23.4% (29 of 124) of tumours showed down regulated HER2/neu expression by IHC. Alterations of HER2/neu IHC scores did not significantly correlate with tumour subtype, pathologic response to NACT, adjuvant regimen, or time interval from the last chemotherapy to surgery. HER2/neu protein overexpression level was associated with favourable pathologic response to anthracycline and taxane-based chemotherapy. However, tumours with altered HER2/neu IHC scores after NACT revealed stable HER2/neu gene amplification/nonamplification by FISH analysis. In conclusion, NACT for breast cancers resulted in the alteration of HER2/neu status by IHC, but tumours were found to have stable gene amplification status by FISH. However, HER2/neu protein overexpression indicated greater sensitivity to neoadjuvant anthracycline- and taxane-based chemotherapy. Thus, retesting HER2/neu IHC status in residual tumours after NACT is recommended in order to optimise adjuvant systemic therapy.

Reviewer's opinion: This study compares the HER2/neu expressions in pre-treatment core biopsy and post-treatment resection specimens containing residual tumour following anthracycline-taxane chemotherapy. The aim was to identify alteration in the HER2/neu receptor status following NACT affecting the decisions to offer adjuvant anti-HER2/neu targeted treatments. The study makes a valid case for assessing HER2/neu status post-NACT as statistically significant changes in ER/PR expression and Ki-67 labeling index after administration of NACT have been identified but the influence of NACT on HER2/neu status however, has not been adequately investigated. The study findings of HER2/neu status affected (down regulated) by NACT might have important clinical consequences for adjuvant systemic treatment and therapy optimisation post surgery. However, the discordance seen on IHC between the pre and post –NACT specimens even though could be related to intratumour heterogeneity, sampling error and technical variability; the influence of these factors in previous studies has been found to minor. Hence, the role of therapeutic agents in down regulation of receptor status assumes a much greater importance. – TH

Neuro-Oncology

Metabolic response of glioma to dichloroacetate measured in vivo by hyperpolarised 13C magnetic resonance spectroscopic imaging

Park JM, Recht LD, Josan S, Merchant M, Jang T, Yen YF, Hurd RE, Spielman DM, Mayer D. Neuro-Oncology 2013;15(4):433-41.

Normal tissues obtain the bulk of energy needs via oxidative phosphorylation (OXPHOS) of multiple energy substrates; solid tumours, including glioma, derive a disproportionate amount of energy via glycolysis, even when oxygen tension levels are high, a phenomenon known as the Warburg effect. This metabolic phenotype of glioma leads to elevated lactate labeling in metabolic imaging using hyperpolarised [1-13C]pyruvate. Although the pyruvate dehydrogenase (PDH)–mediated flux from pyruvate to acetyl coenzyme A can be indirectly measured through the detection of carbon-13 (13C)-labeled bicarbonate, it has proved difficult to visualise 13C-bicarbonate at high enough levels from injected [1-13C]pyruvate for quantitative analysis in brain. In the present study, an optimised protocol for chemical shift imaging and high concentration of hyperpolarised [1-13C]pyruvate were used to improve measurements of lactate and bicarbonate in glioma-transplanted rat brains. Metabolite ratios of lactate to bicarbonate were calculated to provide improved metrics for characterising tumour metabolism. The results showed that glioma and normal brain were well differentiated by lactate-to-bicarbonate ratio, and a stronger response to dichloroacetate (DCA) was observed in glioma than in normal brain. This study suggests that the simultaneous detection of lactate and bicarbonate provides a tool for a more

comprehensive analysis of glioma metabolism and the assessment of metabolic agents as anti-brain cancer drugs.

Reviewer's opinion: Since altered metabolism is a newly recognised hallmark of cancer cells, novel anti-cancer therapies are currently under development aiming to control tumour growth by reversing the Warburg effect. Glioblastoma multiforme is one of the most aggressive cancers and there is a need for methods to assess the effects of therapy acutely after administration, particularly treatments involving metabolic modulation. This study demonstrates for the first time the feasibility of quantitatively detecting 13C-bicarbonate in tumour-bearing rat brain in vivo. Therefore it could have major clinical significance in assessing the efficacy of such therapies. However, it should be recognised that DCA may have very limited clinical applications as an anti-cancer drug due to its toxicity. – QA

Clinical Colorectal Cancer

Treatment of pulmonary colorectal metastases by radiofrequency ablation

Petre E, Jia X, Thornton R et al. Clinical Colorectal cancer 2013;12(1):37-44.

The lung is the second commonest site for colorectal metastases, with 10% of patients developing lung secondaries during the course of their disease. Metastasectomy is generally regarded as the gold standard treatment with reported 5 year survival of 41-56% in selected patients. However many patients are unsuitable for resection due to age, infirmity or lung co-morbidity; recovery may be prolonged and beset by complications. Furthermore, many patients develop further lung lesions and repeat resection is challenging. Previous reports suggest that radiofrequency ablation (RFA) can achieve good local control but numbers are small and follow-up short. This study from Memorial Sloane Kettering Cancer Center in New York looks at 45 patients with a median age of 63 (range 43-81) years who underwent RFA for 69 lung metastases <3.5cm in diameter between 2004 and 2010;. Most had previous or concurrent liver metastases; 36 patients had already undergone chemotherapy and 24 had had surgery for their lung lesions. None were eligible for resection. RFA was delivered to 1-3 lesions in one lung under general anaesthesia on an ambulant basis: where necessary artificial pneumothorax was induced to separate the lesion from mediastinum or chest wall. The commonest complication of RFA was pneumothorax (in a third of patients); there was no mortality associated with treatment. Disease control was monitored by PET/CT at one month and 3-monthly thereafter: median follow-up was 18 months.Nine lesions progressed on follow-up: 4 were successfully retreated, with 92% of patients showing no progression at one year. The median overall survival was 46 months from RFA and 132 months from resection of the colorectal primary. Actuarial survival was 95%, 72% and 50% at 1, 2 and 3 years respectively. The best outcomes were seen in patients with few metastases and those <1.5cm in diameter.

Reviewer's opinion: The limitations of this study are self-evident – it is a retrospective analysis of a relatively small group of patients, treated using a variety of different algorithms. Survival following RFA appears inferior to the best results from metastasectomy, but these figures are achievable only in highly selected patient cohorts and should not be compared to the more familiar patients with multiple metastatic sites and significant comorbidity upon whom this study was based. The authors conclude that RFA can achieve good local control of pulmonary metastases, and propose a randomised comparison with Stereotactic radiotherapy. – JRN