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Prognostic Value of Tumour-Infiltrating Lymphocytes in Triple-Negative Breast Cancers From Two Phase III Randomised Adjuvant Breast Cancer Trials: ECOG 2197 and ECOG 1199

Adams S, Gray RJ, Demaria S, et al. Journal of Clinical Oncology 2014; 20 Sep;32(27):2959-66.

Purpose: Recent studies suggest that tumour-infiltrating lymphocytes (TILs) are associated with disease-free (DFS) and overall survival (OS) in operable triple-negative breast cancer (TNBC). We sought to validate the prognostic impact of TILs in primary TNBCs in 2 adjuvant phase III trials conducted by the Eastern Cooperative Oncology Group (ECOG). **Patients and Methods:** Full-face hematoxylin and eosin–stained sections of 506 tumours from ECOG trials E2197 and E1199 were measured for density of TILs in intraepithelial (iTILs) and stromal compartments (sTILs). Patient cases of TNBC from E2197 and E1199 were randomly selected, based on availability of sections. For the primary end-point of DFS, association with TIL scores was determined by fitting proportional hazards models stratified on study. Secondary end-points were OS and distant recurrence-free interval (DRFI). Reporting recommendations for tumour marker prognostic studies criteria were followed and all analyses were prespecified. **Results:** The majority of the 481 cancers assessed had TILs (sTILs, 80%; iTILs, 15%). With a median follow-up of 10.6 years, higher sTIL scores correlated with better prognosis; for every 10% increase in sTILs, a 14% reduction of risk of recurrence or death (P=0.02), an 18% reduction of risk of distant recurrence (P=0.04), and a 19% reduction of risk of death (P=0.01) were estimated. Multivariable analysis confirmed sTILs are an independent prognostic marker of DFS, DRFI and OS. **Conclusions:** In two national randomised clinical trials using contemporary adjuvant chemotherapy, we have confirmed that stromal lymphocytic infiltration constitutes a robust prognostic factor in TNBCs. Studies assessing outcomes and therapeutic efficacies should consider stratification for this parameter.

Reviewer's opinion: This study addressed the contribution of the immune system to outcome in the least favourable subtype of early stage breast cancer:- a highly topical issue, particularly in view of the emerging efficacy of immune-based therapeutics in many cancers, including PD-1/2 and PD1-2 ligand targeting, Sipuleucel-T (prostate cancer) and ipilimumab (melanoma). Previous studies suggested the predictive and prognostic impact of tumour-infiltrating-lymphocyte (TIL) density in breast cancer in neo-adjuvant and adjuvant settings. The strength of this study is the inclusion of a large number of patients (n=481), a subset with assessable tumour were representative of larger trial population, use of a previously validated simple and reproducible assessment of TIL density with good concordance between two blinded pathologists, and long-term (>10 years) thorough clinical follow-up. The key finding was that stromal TIL density positively correlated with disease-free survival, distant recurrence-free interval and overall survival in both uni- and multi-variate analyses (not including tumour grade). It is notable that the density of intra-epithelial TILs (i.e. those in direct contact with tumour cell islets) was not correlated with clinical outcomes, and was generally low. Therefore further characterisation of the phenotype and function of the stromal TILs is important. It is unexpected that so simple a measure of immune infiltration (CD3 T-cell density) correlates well with outcome, given the diversity of leucocytes present in tumours. Future challenges will be to standardise and possibly automate assessment of TIL density in routine diagnostic histopathology laboratories, and to determine how to combine conventional cytotoxic chemotherapy, targeted therapies directed against defective DNA damage repair (i.e PARP inhibitors) and nascent immunotherapies in this difficult-to-treat and undoubtedly immunogenic cancer. It remains unclear how an estimate of TIL density on a pathology report would change clinical decision-making, although patients with no TIL infiltrate might be considered for trials involving immune-stimulating treatments. – AR

Randomised Phase III trial of Concurrent Acelerated Radiation Plus Cisplatin With or Without Cetuximab for Stage III to IV Head and Neck Carcinoma: RTOG 0522

Ang KK, Zhang Q, Rosenthal DI, et al. Journal of Clinical Oncology 2014; 20 Sep;32(27):2940-50.

Purpose: Combining cisplatin or cetuximab with radiation improves overall survival (OS) of patients with stage III or IV head and neck carcinoma (HNC). Cetuximab plus platinum regimens also increase OS in metastatic HNC. The Radiation Therapy Oncology Group launched a phase III trial to test the hypothesis that adding cetuximab to the radiation-cisplatin platform improves progression-free survival (PFS). **Patients and Methods:** Eligible patients with stage III or IV HNC were randomly assigned to receive radiation and cisplatin without (arm A) or with (arm B) cetuximab. Acute and late reactions were scored using Common Terminology Criteria for Adverse Events (version 3). Outcomes were correlated with patient and tumour features and markers. **Results:** Of 891 patients analysed, 630 were alive at analysis (median follow-up 3.8 years). Cetuximab plus cisplatin-radiation v cisplatin-radiation alone resulted in more frequent interruptions in radiation therapy (26.9 v 15.1%); similar cisplatin delivery (mean, 185.7 v 191.1 mg/m2); and more grade 3 to 4 radiation mucositis (43.2 v 33.3%), rash, fatigue, anorexia, and hypokalemia, but not more late toxicity. No differences were found between arms A and B in 30-day mortality (1.8 v 2.0%, P = 0.81), 3-year PFS (61.2 v 58.9%, P = 0.76), 3-year OS (72.9 v 75.8%; P = 0.32), locoregional failure (19.9 v 25.9%, P = 0.97), or distant metastasis (13.0 v 9.7%, P = 0.08). Patients with p16-positive oropharyngeal carcinoma (OPC) compared with patients with p16-negative OPC had a better 3-year probability of PFS (72.8 v 49.2%, P<0 .001) and OS (85.6 v 60.1%, P<0.001), but tumour epidermal growth factor receptor (EGFR) expression did not distinguish outcome. **Conclusions:** Adding cetuximab to radiation-cisplatin did not improve outcome, and hence should not be routinely prescribed. PFS and OS were higher in patients with p16-positive OPC, but outcomes did not differ regarding EGFR expression.

Reviewer's opinion: This large well-designed clinical trial addressed the issue of optimal treatment for locally-advanced (non-metastatic) squamous cell carcinoma of the larynx, hyphopharynx or oropharynx. Current standard of care is a combination of radiotherapy with concurrent cisplatin chemotherapy based on a meta-analysis of a large number of randomised trials, although in view of more recent results radiotherapy with the anti epidermal-growth-factor-receptor (EGFR) monoclonal antibody cetuximab is an option with good tolerability and little exacerbation of radiotherapy toxicity. In the setting of metastatic or recurrent disease, addition of cetuximab to cisplatin increased the likelihood of response, and addition to cisplatin and 5-FU increased median overall survival. This study therefore compared radiotherapy with cisplatin with or without cetuximab. The treatment delivered reflected modern practice with most patients having had a pre-radiotherapy functional imaging (PET/CT) and over 85% receiving intensity-modulated radiotherapy. There was no suggestion of any benefit of adding cetuximab treatment in terms of local control, distant recurrence or survival, except in patients below 50 years of age. Loco-regional recurrence was more common than distant metastasis. Although tumour tissue was only available for biomarker analysis in 43% of the patients, the findings confirmed that p16 expression portends excellent prognosis (including a lower risk of distant recurrence) in oropharnygeal cancers associated with a lower smoking exposure – probably reflecting a human papilloma virus driven etiology. Cetuximab may have had adverse effects in this group. Chemoradiation using cisplatin is an intensive treatment at the limits of tolerability for many patients, and so it seems logical and plausible that the additional acute toxicity of cetuximab o compromised radiation delivery, accounting for the negative result from the trial. In keeping with this explanation, the rate of loco-regional failure was higher in the cetuximab arm, although the likelihood of distant metastasis was lower. Treatment-related mortality was higher with cetuximab. The authors also suggested that since cetuximab and cisplatin both inhibit the repair of radiation-induced DNA damage, combining cetuximab with a non DNA-damaging chemotherapy agent, such as docetaxel, might be more beneficial. The question of whether radiotherapy concurrent with cisplatin or cetuximab is better remains to be answered. It is possible that tumours with a particular EGFR biology might benefit from the inclusion of cetuximab. – AR

Tumour Stage After Neoadjuvant Chemotherapy Determines Survival After Surgery for Adenocarcinoma of the Esophagus and Esophagogastric Junction

Davies AR, Gossage JA, Zylstra J, et al. Journal of Clinical Oncology 2014; 20 Sep;32(27):2983-90.

Purpose: Neoadjuvant chemotherapy is established in the management of most resectable esophageal and esophagogastric junction adenocarcinomas. However, assessing the downstaging effects of chemotherapy and predicting response to treatment remain challenging, and the relative importance of tumour stage before and after chemotherapy is debatable. **Methods:** We analysed consecutive resections for esophageal or esophagogastric junction adenocarcinomas performed at two high-volume cancer centers in London between 2000 and 2010. After standard investigations and multidisciplinary team consensus, all patients were allocated a clinical tumour stage before treatment, which was compared with pathologic stage after surgical resection. Survival analysis was conducted using Kaplan-Meier analysis and Cox regression analysis. **Results:** Among 584 patients, 400 (68%) received neoadjuvant chemotherapy. Patients with downstaged tumours after neoadjuvant chemotherapy had better survival compared with patients without response (P<0.001), and such downstaging (hazard ratio, 0.43; 95% CI, 0.31 to 0.59) was the strongest independent predictor of survival, after adjusting for age, tumour grade, clinical tumour stage, lymphovascular invasion, resection margin status and surgical resection type. Patients downstaged by chemotherapy compared with patients with no response had lower rates of local recurrence (6 v 13%, P =0.030) and systemic recurrence (19 v 29%, P =0.027) and improved Mandard tumour regression scores (P<0.001). Survival was strongly dictated by stage after neoadjuvant chemotherapy rather than clinical stage at presentation. **Conclusions:** Conclusion The stage of esophageal or esophagogastric junction adenocarcinoma after neoadjuvant chemotherapy determines prognosis rather than the clinical stage before neoadjuvant chemotherapy, indicating the importance of focusing on post-chemotherapy staging to predict more accurately outcome and eligibility for surgery. Patients who are downstaged by neoadjuvant chemotherapy benefit from reduced rates of local and systemic recurrence.

Reviewer's opinion: The prognosis for localised oesophageal cancers remains guarded, although outcomes have improved somewhat with the introduction of neoadjuvant chemotherapy (NACT). This study used retrospective review of a prospectively collected database of newly diagnosed adenocarcinomas of the oesophagus or junctional region, at two institutions, to test the hypothesis that tumour status post chemotherapy governs survival more than initial stage, and that chemotherapy responders have better survival. The control group included patients with very early stage disease (T1/2 N0) and those declining chemotherapy or having medical contraindications to treatment. Patients were clinically staged at presentation using CT or PET/CT and endoscopic ultrasound, and post chemotherapy with CT. Surgical staging used the TMN system and histological regression was graded as per Mandard. Complete microscopic resection was achieved in 60-87% of patients depending on definition with excellent lymph node recovery. Surgical mortality was very low (2.5%) and overall survival was favourable compared to other studies (45% at 5 years). Nearly half the patients receiving chemotherapy had a lower definitive pathological stage than initial clinical stage, and were defined as responders – this group had higher levels of R0 resection, and lower rates of local and systemic recurrence. The vast majority had evidence of at least Mandard grade 1 regression. As anticipated, the post-chemotherapy CT scan was a poor predictor of downstaging effect. In multivariate analyses, chemotherapy response has been an independent predictor of overall survival, and in T3/4 node positive tumours the likelihood of 5-year survival was 52.5% versus 12.6% in responders and non-responders. The implications are clear that advanced imaging procedures, such as 18FDG PET, endoscopic ultrasound or MRI, should be performed post chemotherapy. The ultimate goal would be individualised therapy based on response to NACT with, for example, (i) responding patients undergoing a longer course of treatment, (ii) considering omission of surgery altogether in patients with chemotherapy refractory tumours and (iii) adding radiotherapy in tumours giving a suboptimal response. – AR