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Importance of Surveillance and Success of Salvage Strategies after Definitive Chemoradiation in Patients With Esophageal Cancer

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PURPOSE: Patients with esophageal carcinoma (EC) treated with definitive chemoradiotherapy (bimodality therapy [BMT]) frequently relapse. In a large cohort, we assessed the timing, frequency and types of relapses during an aggressive surveillance program, and the value of the salvage strategies.
PATIENTS AND METHODS: Patients with EC (N = 276) who received BMT were analysed, but not those who had surgery within 6 months of chemoradiotherapy. We focused on local relapse (LR) and distant metastases (DM), and the salvage treatment of patients with LR only. Standard statistical methods were applied.
RESULTS: The median follow-up time was 54.3 months (95% CI, 48.4 to 62.4). First relapses included LR only in 23.2% (n=64), DM with or without LR in 43.5% (n=120), and no relapses in 33.3% (n=92) of patients. Final relapses included no relapses in 33.3%, LR only in 14.5%, DM only in 15.9%, and DM plus LR in 36.2% of patients. Ninety-one percent of LRs occurred within 2 years and 98% occurred within 3 years of BMT. Twenty-three (36%) of 64 patients with LR only underwent salvage surgery, their median overall survival beings 58.6 months (95% CI, 28.8 to - not reached) compared with those patients with LR only unable to undergo surgery (9.5 months; 95% CI, 7.8 to 13.3).
CONCLUSION: Unlike patients undergoing trimodal therapy for whom surveillance/salvage treatment is less important, (1) in the BMT population, ~8% of all patients (or 36% of patients with LR only) with LRs occurring >6 months after chemoradiotherapy can undergo salvage treatment, their survival being excellent. Our data support vigilant surveillance, at least in the first 24 months after chemotherapy, in these patients.
REVIEWERS OPINION: Treatment of clinically localised oesophageal and gastroesophageal junction cancers remains controversial, particularly in the use of trimodal versus bimodal treatment, and the salvage therapy of isolated loco-regional recurrence. Although most studies found that post-operative adjuvant chemoradiation therapy was difficult to deliver and had a high morbidity, pre-operative trearment remains a feasible option. In this study, the majority of patients had adenocarcinoma histology, were male with an average age of 67 years, had tumours of the gastroesophageal junction, about half had poorly differentiated cancers and the majority had AJCC Stage III disease. The surveillance approach was intensive with regular upper GI endoscopic evaluations from multiple biopsies and CT (or preferably CT-PET) imaging. Definitive chemoradiation comprised 50.4 Gy using intensity-modulated radiotherapy or proton beam therapy with concurrent fluoropyrimidine chemotherapy plus either taxanes or platinum agents, although a third of the patients also received induction chemotherapy. Notably, this approach, without primary surgical resection, was associated with long-term disease-free survival in about one third of patients, which compares favourably with outcomes using peri-operative chemotherapy and primary surgery. This study also showed that nearly one-third of patients had persistent locoregional disease, and highlighted the inadequacies of functional imaging and multiple endoscopic biopsies to detect local recurrence early. Although the majority of recurrences were combined distant metastases and loco-regional failure, isolated loco-regional recurrence was not uncommon. The key finding was that in those patients, about one-third could undergo salvage surgery with the vast majority achieving an R0 (microscopically complete) resection and a median survival approaching five years without evidence of increased surgical morbidity or mortality. As 98% of local recurrences occurred within three years, intensive surveillance could reasonably be restricted to this period. Surveillance is, however, costly and anxiety-provoking for patients, making cost-effectiveness and quality-of-life studies relevant. – AR

Incorporation of Pazopanib in Maintenance Therapy of Ovarian Cancer

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Purpose: Pazopanib is an oral multikinase inhibitor of vascular endothelial growth factor receptor (VEGFR) -1/-2/-3, platelet-derived growth factor receptor (PDGFR) -α-α and c-Kit. Preclinical and clinical studies support VEGFR and PDGFR as targets for advanced ovarian cancer treatment. This study assessed pazopanib maintenance therapy in patients with ovarian cancer whose disease did not progress during first-line chemotherapy.
Patients and Methods: Nine hundred and forty patients with histologically confirmed cancer of the ovary, fallopian tube, or peritoneum, at International Federation Gynecology Obstetrics (FIGO) stages II-IV, with no evidence of progression after primary therapy consisting of surgery, and having had least five cycles of platinum-taxane chemotherapy were randomised 1:1 to receive pazo-

panib 800 mg once per day or placebo for up to 24 months. The primary end-point was progression-free survival by RECIST 1.0.
Results: Maintenance pazopanib prolonged progression-free survival compared with placebo (hazard ratio [HR], 0.77; 95% CI, 0.64 to 0.91; P = 0.0021; median, 17.9 v 12.3 months, respectively). Interim survival analysis based on events in 35.6% of the population were not significantly different. Grade 3 or 4 adverse events of hypertension (30.8%), neutropenia (9.9%), liver-related toxicity (9.4%), diarrhoea (8.2%), fatigue (2.7%), thrombocytopenia (2.5%), and palmar-plantar erythrodysesthesia (1.9%) were significantly higher in the pazopanib arm. Treatment discontinuation resulted on more adverse events ing patients treated with pazopanib (33.3%) (placebo 5.6%).
Conclusion: Pazopanib maintenance therapy provided a median improvement of 5.6 months (HR, 0.77) in progression-free survival in patients with advanced ovarian cancer who have not progressed after first-line chemotherapy. Overall survival data to this point did not suggest any benefit. Additional analysis should help to identify subgroups of patients in whom improved efficacy may balance toxicity
REVIEWERS OPINION: Optimal debulking surgery and peri-operative platinum and taxane based chemotherapy remain the cornerstones of treatment of advanced ovarian cancer, achieving long-term survival in perhaps one in 3 patients. Treatment of platinum resistant disease remains very challenging, with modest palliative benefits of further chemotherap, such as liposomal doxorubicin, weekly paclitaxel, or topotecan. Anti-angiogenic therapies have begun to be effective in ovarian cancer. In the ICON-7 study, there was a 5-6 month improvement in median progression-free and overall survival with concurrent and maintenance bevacizumab (anti-VEGF-A monoclonal antibody) in the first line setting in patients with Stage IV disease and Stage III with over 1cm residual lesions post-operatively. The oral VEGFR tyrosine kinase inhibitor, cediranib, given concurrently with chemotherapy and as maintenance treatment increased median overall survival by almost 3 months in women with platinum sensitive relapsed ovarian cancer in the ICON-6 study, and encouraging findings on bevacizumab are also emerging in the platinum resistant context from the AURELIA study. This well designed randomised study compared the predominantly anti-angiogenic tyrosine kinase inhibitor, pazopanib, already in use in metastatic renal cell carcinoma and soft-tissue sarcoma, with placebo after non-progression on completion of first line therapy in advanced ovarian cancer. Treatment continued until progression. About 85% of patients had no evidence of disease radiologically or biochemically after surgery and chemotherapy, and almost 60% of patients achieved complete macroscopic resection whether with primary or delayed debulking surgery. Trial treatment generally started within 2 months of the final dose of chemotherapy. The key findings were that pazopanib maintenance therapy increased median progression-free survival by 5.6 months with no effect on median overall survival. Moreover, the PFS benefit was restricted to patients of non-East Asian ethnicity, with a detrimental effect in East Asian patients possibly due to higher rates of drug discontinuation and dose reduction, which may reflect inter-ethnic pharmacogenetic differences. The toxicity profile was that expected from other trials, with fatigue, hypertension, abnormal transaminases, diarrhoea and hand-foot syndrome, although there were higher than expected rates of neutropenia perhaps related to recent cytotoxic chemotherapy (which would not have been the case in the renal cell carcinoma trials). This study showed the biological activity of pazopanib in this setting; treatment did delay the time to 2nd line chemotherapy (reflecting perhaps the time to symptomatic progression), although it will be interesting to see the effects on quality of life and whether concurrent and maintenance treatment is needed to increase overall survival - AR

Combined BRAF (Dabrafenib) and MEK Inhibition (Trametinib) in Patients with BRAFV600-Mutant Melanoma Experiencing Progression with Single-Agent BRAF inhibitor

Johnson DB, Flaherty KT, Weber JS, et al. Journal of Clinical Oncology 2014; 20 Nov; 32(33):3697-704.

PURPOSE: Preclinical and early clinical studies have demonstrated that initial therapy with combined BRAF and MEK inhibition is more effective in BRAF(V600)-mutant melanoma than single-agent BRAF inhibitors. This study assessed the safety and efficacy of dabrafenib and trametinib in patients who had received prior BRAF inhibitor treatment.
PATIENTS AND METHODS: In this open-label phase I/II study, we evaluated the pharmacology, safety and efficacy of dabrafenib and trametinib. Patients treated with combination therapy after disease progression with BRAF inhibitor treatment administered before study enrollment (part B; n = 26) or after cross-over at progression with dabrafenib monotherapy (part C; n = 45).
RESULTS: In parts B and C, confirmed objective response rates (ORR) were 15% (95% CI, 4 to 35%) and 13% (95% CI, 5 to 27%), respectively; an additional 50% and 44% experienced stable disease ≥8 weeks, respectively. In part C, median progression-free survival (PFS) was 3.6 months (95% CI, 2 to 4), and median overall survival was 11.8 months (95% CI, 8 to 25) from cross-over. Patients who previously received dabrafenib ≥6 months had better outcomes with the combination compared with those treated <6 months; median PFS was 3.9 (95% CI, 3 to 7%) versus 1.8 months (95% CI, 2 to 4%; hazard ratio, 0.49; P = 0.02), and ORR was 26% (95% CI, 10 to 48%) versus 0% (95% CI, 0 to 15%).
CONCLUSION: Dabrafenib plus trametinib has modest clinical efficacy in patients with BRAF inhibitor-resistant melanoma. This regimen may be a therapeutic strategy for patients who previously benefited from BRAF inhibitor monotherapy ≥6 months, but demonstrates minimal efficacy after rapid progression with BRAF inhibitor therapy.

The range of therapeutic options for patients with metastatic melanoma has expanded greatly in recent times. Previously, the two approved treatments were dacarbazine chemotherapy - with a low objective response rate and no evidence of survival benefit, and high-dose interleukin 2 that can lead to durable regressions in the face of significant toxicity. Over the last decade, however, an improved understanding of the molecular pathogenesis of the disease and also tumour immunology has led to the development and approval of ipilimumab (anti-CTLA-4), dabrafenib and vemurafenib (RAF inhibitors), trametinib (MEK inhibitor) and latterly pembrolizumab (anti-PD-1). RAF and MEK inhibitors target the MAP kinase pathway at different points, but the role of MEK inhibitors remains unclear in the clinical context. In the first line setting, trametinib proved superior to chemotherapy (dacarbazine/paclitaxel) in the METRIC study in patients with codon 600 BRAF mutation, and evidence is emerging that first-line treatment with combined RAF/MEK blockade may be better than single-agent RAF inhibition, although Phase III evidence is awaited. This study addressed the important question of treatment after failure of first-line single-agent RAF inhibitor therapy which typically occurs within seven months of treatment initiation. The results confirmed that trametinib and dabrafenib could be safely delivered together with

a reduced risk of squamous cell carcinoma and keratoacanthoma, but fever and cardiac dysfunction were noted toxicities. In terms of efficacy, approximately half of patients had stable disease for at least 8 weeks, although the response rate was low. The key finding was in patients with delayed resistance (>6 months) to single-agent RAF inhibitor, the response rate being 26%, with one complete response, and median progression-free survival was ~4 months. These clinical findings are consistent with pre-clinical data that, in terms of resistance to RAF inhibitor therapy, secondary N-RAS mutation is uncommon and typically develops late after >6 months of therapy, and patients with N-RAS mutations can respond to MEK inhibition. Investigating the mechanisms of acquired resistance to targeted therapy in melanoma remains very high priority, which will help design strategies that delay or prevent it. We also must get a better understanding of the interaction between small molecular inhibitors and immunotherapy, which might allow rational design of combinatorial approaches. – AR

Neuro Oncology

The combination of IDH1 mutations and MGMT methylation status predicts survival in glioblastoma better than either IDH1 or MGMT alone.

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Glioblastoma, the most common malignant brain tumour, has a poor prognosis. Most glioblastomas are primary, ie they manifest rapidly de novo without recognisable precursor lesions. Approximately 5% of glioblastomas are diagnosed in patients with a preceding low-grade glioma that has progressed to secondary glioblastoma over a period of years. Both genotypes are considered to be histopathologically indistinguishable, but differences in molecular alterations are apparent. Genetic and epigenetic profiling of glioblastomas has provided a comprehensive list of altered cancer genes of which only O6-methylguanine-methyltransferase (MGMT) methylation is used so far as a predictive marker in a clinical setting. This study investigated the prognostic significance of genetic and epigenetic alterations in glioblastoma patients by screening 98 human glioblastoma samples for alterations in 10 genes and chromosomal loci by PCR and multiplex ligation-dependent probe amplification (MLPA). Data analyses showed that mutations in isocitrate dehydrogenase 1 (IDH1), promoter methylation of MGMT, irradiation dosage, and Karnofsky Performance Status (KFS) were independent prognostic factors. A 2-gene predictor for glioblastoma survival was generated. Based on the genetic and epigenetic status of IDH1 and MGMT, glioblastoma patients were stratified into 3 clinically different genotypes: glioblastoma patients with IDH1mt/MGMTmet had the longest survival, followed by patients with IDH1mt/MGMTunmet or IDH1wt/MGMTmet, and patients with IDH1wt/MGMTunmet had the shortest survival. This 2-gene predictor was an independent prognostic factor and was significantly better at predicting survival than either IDH1 mutations or MGMT methylation alone. The predictor was also validated in 3 external datasets.

Reviewer's opinion: MGMT methylation is a predictive factor in the response of glioblastoma patients to temozolomide and radiotherapy, and hence their survival. However, conflicting results have been reported on the methylation status of MGMT as a positive prognostic marker independent of therapy, new and more effective prognostic biomarkers being needed. Recently, mutations of the IDH1 and IDH2 genes have been identified in a subset of glioblastoma. Notably, IDH1/2 mutations occur predominantly in younger patients and secondary glioblastomas. IDH1, but not IDH2, mutations are independent positive prognostic markers for glioblastoma patient survival. The study indicates that the combination of IDH1 mutations and MGMT methylation status predicts survival in glioblastoma patients better than either IDH1 or MGMT alone. The finding is interesting and might provide certain guideline in clinical practice. – QA