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Success with combination therapy for neuroendocrine cancer

New data from the randomized, double-blind, placebo-controlled, multicentre phase III RADIANT-2 trial has revealed that combination therapy with a rapamycin-derived immunosuppressant, everolimus, and the somastatin analogue, octreotide LAR, lengthens median progression-free survival in patients with advanced neuroendocrine tumours.

Dr James Yao, Associate Professor, MD Anderson Cancer Centre, University of Texas, Houston, Texas, reported that patients who received the everolimus–octreotide LAR combination had a median progression-free survival of 16.4 months *vs* 11.3 months in patients assigned to placebo plus octreotide LAR.

'Conventional chemotherapy has limited efficacy for patients with advanced neuroendocrine tumours, and there remains a significant unmet medical need in this population,' he commented.

While the everolimus and octreotide LAR combination did not achieve its primary progression-free survival end point, the 5.1-month increase in progression-free survival is a clinically meaningful improvement.

Importantly, analyses that adjusted for imbalances in baseline characteristics in the two treatment groups and inconsistencies in the review of radiology scans for disease progression showed that everolimus plus octreotide LAR significantly decreased the likelihood of disease progression.

A total of 429 patients with advanced low- or intermediate-grade neuroendocrine tumours and a history of symptoms attributed to carcinoid syndrome were randomized to treatment with oral everolimus (10 mg/day) plus octreotide LAR (30 mg administered by intramuscular injection every 28 days) or placebo plus octreotide LAR. Treatment continued until disease progression.

Dr Yao said that octreotide LAR has been the foundation of therapy for patients with neuroendocrine tumours, but additional treatment options were needed. Everolimus, an oral inhibitor of mTOR, had demonstrated promising anti-tumour activity in patients with neuroendocrine tumours as a single agent and in combination with octreotide LAR in two phase II studies.

The difference in median progression-free survival between the two arms of RADIANT-2 represented a 23% reduction in risk of progression (hazard ratio=0.77, P=0.026).

Correcting for the informative censoring bias, further analysis showed a significant 5.5-month improvement in median progression-free survival with the combination treatment (hazard ratio=0.60, P= 0.0014).

The benefit of the everolimus–octreotide LAR combination was seen across all patient sub-groups. Most frequent drug-related adverse events were stomatitis, rash, fatigue, and diarrhoea; mostly grade 1–2. Grade 3–4 adverse events reported in >5% were stomatitis, fatigue, diarrhoea, infections and hyperglycaemia.

Dr Yao concluded: 'The combination of everolimus and octreotide LAR provided a 5.1-month clinically meaningful increase in median progression-free survival – a benefit that increased to 5.5 months after correcting for reporting bias.'

Stephen Pinn

Adjuvant chemotherapy no benefit in patients with rectal cancer

Patients with pathological complete response or ypT3-4 residual tumour after neo-adjuvant chemoradiation for rectal tumour do not seem to benefit from adjuvant chemotherapy.

This was the main finding of a large-scale analysis of patient data, reported by Dr Geerard Beets of the University Medical Centre, Maastricht, The Netherlands.

Dr Beets said these discouraging data might be the result of the already good prognosis of patients with pathological complete response and less responsiveness to 5-fluorouracil-based chemotherapy in the poor responders (the ypT3-4 tumours).

He explained there was a possibility that adjuvant chemotherapy could be omitted or adapted for these patients – also that patients with ypT1-2N0 appear to benefit most from adjuvant chemotherapy.

Dr Beets added that chemoradiation for rectal cancer increasingly results in pathological response. It has been suggested that patients with different degrees of response might not have the same benefit of adjuvant chemotherapy.

The aim of this study was to determine whether patients with a pathological complete response, ypT1-2 or ypT3-4 tumour after chemoradiation for rectal cancer have different benefits of adjuvant chemotherapy for disease-free survival.

Authors from studies evaluating different degrees of response to chemoradiation were contacted to share individual patient data, and the collected individual patient data were pooled into one dataset.

A total of 2724 patients were included – 811 had pathological complete response (30%), 863 had ypT1-2 (32%) and 1050 had ypT3-4 (39%).

During a median follow up of 50 months, 41% of patients underwent adjuvant chemotherapy, which consisted mostly of 5-fluorouracil-based chemotherapy.

The hazard ratio for disease-free survival for adjuvant chemotherapy was 0.94 for patients with pathological complete response, 0.61 for patients with ypT1-2 tumours and 0.97 for patients with ypT3-4 tumours.

Meanwhile, ypT1-2N0 patients benefited most from adjuvant chemotherapy (hazard ratio 0.45 *vs* 0.79 for patients with ypT1-2N+. For ypT3-4 patients pN-stage did not alter the benefit of adjuvant chemotherapy.

Stephen Pinn