Methylation of somatostatin receptor 2 gene in neuroendocrine tumours as a predictor of tumour response to peptide receptor radionuclide therapy

Authors: Shamus Butt,[A] Joanne Evans,[B] Francesco Mauri[B] and Rohini Sharma[B]

Aims

Somatostatin receptors are a fundamental target for treating neuroendocrine tumours (NETs) with 'cold' or 'hot' somatostatin analogues. Metastatic NETs progressing after medical therapy can receive peptide receptor radionuclide therapy (PRRT) on the precondition that patients exhibit positive radiotracer uptake using ^{68}Gallium-DOTA^{0}-Tyr^{3}-octreotate positron emission tomography / computed tomography imaging. However, the confirmation of somatostatin receptor 2 (SSTR2) as evidenced by the positive imaging fails to translate into treatment efficacy for PRRT pursuing the same pathway. Moreover, there is a lack of predictors of response to this highly expensive treatment. Studies have established that positive radiotracer uptake is associated with better treatment outcomes. The aim of this study was to ascertain the relationship between promoter methylation in the *SSTR2* gene with SSTR2 expression and tumour response to PRRT.

Methods

Methylation analysis of the upstream promoter region of the *SSTR2* gene was conducted on 27 samples from patients with advanced NETs and treated with PRRT from 2008 to 2016. Tissue microarray blocks were constructed and sections were immunostained for SSTR2 using the UMB-1 antibody.

Results

Twenty-seven cases were identified: 51% male, mean age 55 years ±13.4. One-hundred per cent presented with metastatic disease. Thirty-three percent of cases were from small bowel primary NET. Five samples were lost due to inadequate quality. Median methylation of the *SSTR2* promoter in patient samples was 12.38%, significantly higher than controls (5.21%, p=0.006). A significant difference in *SSTR2* promoter methylation was observed in patients who respond to PRRT in contrast to non-responders (12.17% vs 15.18%, p=0.047).

Conclusion

A hypermethylated state of the *SSTR2* gene promoter region may be associated with reduced response to PRRT. Future studies should ascertain a suitable cut-off for methylation status that could stratify patients for those that may have increased likelihood in responding to PRRT. Epigenetic drugs should be explored for potential utility in selectively modifying the silenced epigenetic state of the *SSTR2* promoter. ■

Conflict of interest statement

None declared.

Authors: [A]University of Bristol, Bristol, UK; [B]Surgery and Cancer, Imperial College London, London, UK