Radionuclide therapy in neuroendocrine tumours: a systematic review
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CRD summary
The authors concluded that no strong evidence existed to support that one therapeutic radiopharmaceutical was more effective than others. The authors' conclusions seem to reflect the variable evidence presented but limitations of the review synthesis and a lack of detail about the study quality assessment results make the reliability of the authors' conclusions uncertain.

Authors' objectives
To investigate the effects of therapeutic radiopharmaceuticals in patients with different types of advanced neuroendocrine tumour.

Searching
MEDLINE and EMBASE were searched from January 1998 to November 2010 for full text reports published in English; search terms were reported. The Cochrane Library (issue 10, 2010), SAGE (from January, 2003, to June, 2010) and bibliographies of included studies were searched for further studies.

Study selection
Eligible studies included clinical practice guidelines based on systematic reviews, randomised controlled trials and prospective or retrospective studies. Also included were prospective studies with 30 or more patients and retrospective studies with 100 or more patients. Eligible studies compared or reported the effects of any of the prespecified therapeutic radiopharmaceuticals on any of the clinical outcomes of complete response, minor response, partial response, stable disease, progression-free survival, overall survival, quality of life and toxicity.

Two thirds of the included studies investigated peptide receptor radionuclide therapies (PRRT) and one third investigated metaiodobenzylguanidine (I-MIBG) treatment. PRRTs investigated were In-DTPAOC, Y-DOTALAN, Y-DOTATOC, Y-DOTATATE, and Lu-DOTATATE. Participant age ranged from 18 to 88 years for PRRT studies and from 0.5 to 77 years for I-MIBG studies. Most PRRT patients had various types of neuroendocrine tumours; most I-MIBG patients had neuroblastoma tumours. Tumour stages tended to be III or IV. Patients had frequently had prior treatments, which included surgery, chemotherapy, biotherapy, octreotide, external beam radiation and combinations of these therapies. Almost all patients had never before received PRRT or I-MIBG treatments.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Study quality was assessed using the Newcastle-Ottawa Scale to assess quality according to selection, comparability, and exposure. Possible scores ranged from zero to a maximum of 9 for the highest quality.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Outcomes (survival rate/time, response rates, quality of life ratings and toxicity-related events) were extracted.

The authors did not state how many reviewers extracted the data.

Methods of synthesis
Outcomes were categorised according to their administration of PRRT or I-MIBG and synthesised narratively. Overall response rates were presented as percentages with 95% confidence intervals (CIs).

Results of the review
Twenty-four studies were included in the review (1,791 patients, range 30 to 504): 16 PRRT studies (1,179 patients) and eight I-MIBG studies (612 patients); 22 studies were prospective. The authors reported that the overall study quality
ratings ranged from poor to moderate. Twenty-two studies clearly recorded treatment doses and schemas of radionuclide therapy, one reported blinding, 18 had sufficient follow-up time and 23 analysed 80% or more of the patients for at least one clinical outcome. The authors reported that a detailed table of study quality results was available on request but this could not be obtained.

**Survival time/rate:**

Six PRRT studies reported median overall survival time, which ranged from 16 months for patients treated with Y-DOTATOC to 46 months for patients treated with Lu-DOTATATE. Median survival time was 15 months for patients who had received a second treatment of Lu-DOTATATE following progression of their disease.

In one study (31 patients) no statistically significant difference was found between intervention (treated with In-DTPAOC or I-MIBG) and control (no treatment) groups for progression-free and overall survival rates. Three studies reported that patients with a complete response, partial response or stable disease after PRRT had a longer overall survival time than patients with progressive disease.

For I-MIBG studies median survival rates among stage III-IV neuroblastoma patients (median age of two to 6.6 years; three studies) were 49% at year one and 29% at year two for one study. An earlier study by the same authors demonstrated an overall median survival rate of six months with patients of the same condition and a similar age. One study demonstrated no statistically significant difference in overall survival rate at five years between intervention (I-MIBG treatment) (63%, 95% CI 47% to 75%) and control (no treatment) groups (47%, 95% CI 34% to 59%) for patients with progressive stage IV midgut carcinoid (p=0.10).

One study demonstrated that progression-free survival rates at five years ranged from 40% (95% CI 24% to 56%) with stage IV patients to 92% (95% CI 78% to 100%) with stage III neuroblastoma patients.

**Response on imaging:**

Comparison of PRRT studies was difficult due to different criteria being used for evaluation of tumour response and different definitions for partial response, stable disease and progressive disease.

For In-DTPAOC (two studies) the overall response rates were 5% (95% CI 0% to 15%) and 18% (95% CI 6% to 30%) for patients with various progressive stage III-IV neuroendocrine tumours.

For Y-DOTATOC (six studies) overall response rates ranged from 4% (95% CI 0% to 8%) with various progressive stage IV carcinoid patients to 28% (95% CI 19% to 37%) for patients with various mixed-status stage III-IV neuroendocrine tumours.

For Y-DOTALAN (one study) the overall response rate for carcinoid patients was 18% (95% CI 5% to 31%).

For Y-DOTATATE (two studies) overall response rates were 44% (95% CI 27% to 61%) for patients with various stage IV neuroendocrine tumours and 23% (95% CI 12% to 34%) for patients with various stage IV gastroenteropancreatic neuroendocrine tumours.

For Lu-DOTATATE (two studies) overall response rates ranged from 24% (95% CI 9% to 39%) for patients with various stage IV gastroenteropancreatic neuroendocrine tumours to 75% (95% CI 51% to 100%) for gastrinoma patients.

Six of the eight I-MIBG studies assessed tumour response on imaging; different criteria were used across the studies. Overall response rate ranged from 26% (95% CI 13% to 39%) for patients with various stage III-IV neuroendocrine tumours to 75% (95% CI 62% to 88%) with stage III-IV neuroblastoma patients.

**Quality of life:** Quality of life improved for some patients in all seven of the PRRT studies that assessed it; comparisons between studies and different therapeutic radiopharmaceuticals could not be made due to clinical differences. No quality of life assessments were reported in any of the I-MIBG studies.
Toxicity:

For PRRT studies, severe toxicities included: development of myelodysplastic syndrome (MDS) and/or leukaemia (8% in one study) with In-DTPAOC; grade 4 renal toxicity (0.9% to 3.4% across three studies) and MDS (2% in one study) with Y-DOTATOC; and grade 2 renal toxicity (30% in one study), renal insufficiency (0.4% in one study), hepatic insufficiency (0.6% in one study) and MDS (0.8% in one study) for Lu-DOTATATE. Studies that investigated the efficacy of Y-DOTATOC, Y-DOTATATE and Lu-DOTATATE infused lysine and arginine amino acid solution to protect patients' kidney function.

For I-MIBG studies, severe toxicities included: bone marrow replacement; primary or secondary leukaemia; MDS; leukaemia; secondary malignancies (among three to five year old children with stage III-IV neuroblastoma); and death. Proportions of patients who developed these conditions ranged from 0.3% to 43% (results from individual studies are reported in the paper).

Further results from all of the outcomes were reported fully in the paper.

Authors’ conclusions

Peptide receptor radionuclide therapy seemed to be an acceptable option and was relatively safe in adult advanced neuroendocrine tumour patients with receptor positive uptake on scintigraphy but patients' renal function must be monitored. There was no strong evidence that one therapeutic radiopharmaceutical was more effective than others.

CRD commentary

The review question was clear. Inclusion criteria appeared sufficiently replicable. Relevant databases were accessed. Only studies in English were eligible for selection so some relevant studies may have been missed. An appropriate quality assessment tool was used and study quality was variable. The authors did not state how many reviewers were involved in study selection, data extraction and quality assessment so risks of error and bias during the review process was unclear. Study details provided were adequate. A narrative synthesis was performed, which appeared appropriate considering the clinical and methodological heterogeneity across studies. The synthesis largely comprised presentation of ranges with little or no reference to the study quality assessment (most studies had no comparison group, which made it difficult to interpret the meaning of results).

The authors' conclusions seem to reflect the variable evidence presented but limitations of the review synthesis and a lack of detail about the study quality assessment results mean that the reliability of the authors' conclusions is uncertain.

Implications of the review for practice and research

Practice: PRRT seemed to be acceptable and relatively safe in adult patients with advanced neuroendocrine tumours and with receptor uptake positive on scintigraphy but renal functioning of patients must be monitored. I-MIBG may be effective for malignant neuroblastoma, paraganglioma or pheochromocytoma but its side effects must be considered.

Research: The authors stated that well-designed and good quality randomised controlled trials were required to investigate the efficacy of PRRT in neuroendocrine cancer patients and the efficacy of I-MIBG in patients with malignant neuroendocrine tumours with negative uptake on octreotide scintigraphy or renal insufficiency and positive uptake on I-MIBG or I-MIBG scintography.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.