Everolimus, lutetium-177 DOTATATE and sunitinib for advanced, unresectable or metastatic neuroendocrine tumours with disease progression: a systematic review and cost-effectiveness analysis

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Scientific summary

Three interventions for treating neuroendocrine tumours

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Scientific summary

Background

Neuroendocrine tumours (NETs) are heterogeneous cancers that develop in the cells of the diffuse neuroendocrine system. The aetiology is poorly understood; however, NETs typically develop slowly and may remain undetected over a number of years.

The characteristics of a NET (e.g. location, grade and differentiation, stage of tumour and secretory profile) will determine the methods of treatment and affect prognosis. Prognosis is generally better with an early diagnosis; however, NETs are commonly diagnosed at a later stage when they have already metastasised.

Between 2013 and 2014, 8726 neoplasms were diagnosed in England. Diagnosing NETs can be difficult as they are often small tumours (< 1 cm in size) and they can occur almost anywhere in the body and present with a vast array of symptoms (typically non-specific symptoms such as pain, nausea or vomiting) or no symptoms at all.

The aim of treatment should always be curative. However, in the majority of cases it is most likely to be palliative. As metastatic disease is common, improving quality of life is often the primary aim of treatment. Individuals with NETs can maintain a good quality of life for a long period of time.

There are many treatment options for NETs. Initial treatment starts with surgery and symptom management, after which treatment may include liver transplant, interferon alpha (Roferon-A, Roche Products Ltd), chemotherapy, ablation therapies, targeted radionuclide therapy [including lutetium-177 DOTATATE (177Lu-DOTATATE) Lutathera®; Imaging Equipment Ltd, Radstock, UK)], transhepatic artery embolisation/ chemoembolisation, external-beam radiotherapy and emerging therapies [including everolimus (Afinitor®; Novartis International AG, Basel, Switzerland) and sunitinib (Sutent®; Pfizer Inc., New York, NY, USA)].

Objectives

The objectives of this study were to, first, estimate the clinical effectiveness of three interventions (everolimus, 177Lu-DOTATATE and sunitinib) for treating unresectable or metastatic NETs with disease progression and, second, establish the cost-effectiveness of these interventions.

Changes in project scope

During the course of this project, the National Institute for Health and Care Excellence (NICE) consulted on amendments to the original project scope. The revised scope was agreed on 18 August 2016 and the intervention lanreotide (Somatuline Autogel®; Ipsen, Paris, France) and the comparator octreotide (Sandostatin®; Novartis) were removed.

Methods

The assessment comprises a systematic review of clinical effectiveness and cost-effectiveness studies, a review and critique of the company submissions and a de novo economic analysis.

Clinical effectiveness systematic review

A systematic review, following methodological guidance from the Centre for Reviews and Dissemination, was used to assess the clinical effectiveness evidence on everolimus, 177Lu-DOTATATE and sunitinib for treating unresectable or metastatic NETs with disease progression.

Identification of studies

Literature searching of seven bibliographic databases (including MEDLINE and EMBASE), four trial registries (including Current Controlled Trials and ClinicalTrials.gov) and two websites [the European Neuroendocrine Tumor Society [see www.enets.org/ (accessed 19 May 2016)] and the UK and Ireland Neuroendocrine Tumour Society [see www.ukinets.org/ (accessed 19 May 2016)], and additional supplementary search methods, were used for the identification of clinical effectiveness studies.

Study selection

- Population: people with progressed unresectable or metastatic NETs in locations covered by existing and anticipated marketing authorisations for the interventions.
- Interventions: everolimus [pancreatic, gastrointestinal (GI) or lung NETs], 177Lu-DOTATATE (pancreatic or GI NETs) and sunitinib [pancreatic NETs (pNETs)].
- Comparator: another intervention or interferon alpha, chemotherapy regimens and/or best supportive care (BSC).
- Outcomes: overall survival (OS), progression-free survival (PFS), response rates (RRs), symptom control, adverse events (AEs) and health-related quality of life (HRQoL).

Titles and abstracts were independently double-screened by two reviewers for inclusion and disagreements were resolved by discussion. Studies meeting the inclusion criteria at the title and abstract stage were double-screened at the full-text stage.

Data analysis/synthesis

The methodological quality of each included study was assessed and data were extracted, tabulated and narratively synthesised. When the data allowed, indirect treatment comparisons (ITCs) were performed using the Bucher method.

Cost-effectiveness systematic review

Cost-effectiveness studies were reviewed in accordance with the methods used in the systematic review of clinical effectiveness, extended to include electronic searches of bibliographic databases of health economic studies. In addition to economic evaluation studies, costing studies in UK settings were included. Only full texts were included, but relevant UK studies reported in conference posters were considered as supplementary information.

Results

Clinical effectiveness systematic review

Number and quality of effectiveness studies

Of 6209 titles/abstracts screened, three trials, RADIANT-3 (RAD001 in Advanced Neuroendocrine Tumors, Third Trial), A6181111 and RADIANT-4 (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial), met the inclusion criteria for the review.

A fourth trial, NETTER-1 (Neuroendocrine Tumors Therapy), was identified under the original scope but excluded under the revised scope as it no longer met the inclusion criteria. This randomised controlled trial (RCT) compared 177Lu-DOTATATE with 60 mg of octreotide. The Assessment Group appreciate that this trial might be of interest to the committee and, following a request from NICE, the results and comparative analysis are presented within the report.

The risk of bias in all three included studies was low.

Summary of benefits and risks

Pancreatic neuroendocrine tumours

Evidence consistently suggested a treatment effect for pNETs in favour of both everolimus (RADIANT-3; $n = 410$) and sunitinib (A6181111; $n = 171$) compared with placebo for the outcomes of interest. Treatment switching from the placebo arm to the treatment arm occurred in 73% of participants in RADIANT-3 and 69% in A6181111. The treatment switching significantly compromised the OS results. Overall, AEs were more commonly reported following treatment with everolimus and sunitinib than following treatment with placebo.

Indirect treatment comparison for pancreatic neuroendocrine tumours

The ITC for PFS from central radiology review suggests that there is no difference between the treatments [hazard ratio (HR) 1.06, 95% confidence interval (CI) 0.57 to 1.97], whereas the ITC for PFS from local review suggests that everolimus is associated with a 17% decrease in disease progression or death compared with sunitinib (HR 0.83, 95% CI 0.49 to 1.42). However, the 95% CI is consistent with there being no difference in PFS effectiveness between everolimus and sunitinib.

For OS, the ITC suggests that there is a 2.56 times greater hazard of dying in the everolimus treatment group than in the sunitinib treatment group, which is statistically significant. However, these analyses were not adjusted for treatment switching after disease progression and should not be relied on.

For RRs, the ITC suggests that there is an 82% increase in the odds of a partial response in individuals treated with sunitinib compared with those treated with everolimus. However, sunitinib was associated with a 52% increase in the odds of progressive disease compared with everolimus. Everolimus was associated with a 2.3 times greater odds of disease stability than sunitinib. However, all of these ITCs were associated with wide 95% CIs, suggesting that there is little evidence of a difference in RRs between everolimus and sunitinib.

Gastrointestinal and lung neuroendocrine tumours

Evidence consistently suggested a treatment effect for GI and lung NETs in favour of the use of everolimus (RADIANT-4; $n = 302$) compared with placebo for the outcomes of interest. A limitation was the immaturity of the OS data and bias from treatment switching in the control arm.

Cost-effectiveness systematic review

Four studies were identified, all of which were carried out with patients with advanced pNETs. Two studies were model-based cost–utility analyses of sunitinib plus BSC compared with BSC based on the A6181111 trial data. Another study was a model-based cost–utility analysis of everolimus compared with sunitinib, which used effectiveness data from a matched adjusted indirect comparison of the RADIANT-3 and A6181111 trials. The fourth study was a model-based cost–utility analysis of sunitinib plus BSC compared with BSC. All of these studies used the same semi-Markov model structure of three health states (stable disease, progressive disease and death) and used parameter values derived from partitioning of parametric OS curves between those states using parametric PFS curves. All of these studies were sponsored by the manufacturers of the respective treatments under evaluation.

The study of everolimus compared with sunitinib found that the incremental cost-effectiveness ratio (ICER) for everolimus compared with sunitinib was equivalent to £30,524 at 2010 US prices, whereas the studies that compared sunitinib plus BSC with BSC found that sunitinib plus BSC had a discounted cost per quality-adjusted life-year (QALY) gained relative to BSC of £22,587. This result allowed for an adjustment for crossover to active treatment in the placebo plus BSC arm of A6181111.

The studies had severe limitations primarily as they were based only on Phase III trials with no active treatment comparators. The generalisability of these findings to the NHS remains in question, particularly as a conference abstract was the only identified report of a study in a UK setting.

Peninsula Technology Assessment Group de novo economic model and evaluation

We undertook a de novo cost-effectiveness analysis of the following decision problems:

- pNETs:
  - everolimus plus BSC
  - sunitinib plus BSC
  - BSC alone
- GI and lung NETs:
  - everolimus plus BSC
  - BSC alone
- GI (midgut) NETs:
  - everolimus plus BSC
  - 177Lu-DOTATATE plus 30 mg of octreotide (included as an intervention in scenario analyses)
  - BSC alone.

The choice of these tumour locations was determined by the available effectiveness data identified in the published literature. We did not perform subgroup analyses specified in our protocol because of the lack of data reported in suitable form from effectiveness sources. We did not have access to individual patient data (apart from A6181111) but extracted them from Kaplan–Meier curves.

We assumed that patients started treatment aged 60 years and assumed a 40-year time horizon. Costs and QALYs were discounted at 3.5% per annum. Analyses were undertaken using the same three-health-state model structure used in the economic evaluation literature and we assumed partitioned survival using summary data on PFS, OS and time on treatment outcomes in RADIANT-3 and A6181111 (pNETs), RADIANT-4 [GI and lung NETs and GI (midgut) NETs] and NETTER-1 [scenario analysis of GI (midgut) NETs including 177Lu-DOTATATE]. We used OS data that were adjusted by the rank-preserving failure time model whenever available.

We extrapolated observed PFS and OS in the RCTs by estimating parametric distributions of recreated individual patient time to event PFS and OS data from those trials. For the indirect comparison in pNETs, we adjusted the PFS and OS for sunitinib by the relative difference in the restricted mean time to event for the respective outcome between the placebo arm in RADIANT-3 and the placebo arm in A6181111.

We measured the costs of drug administration and acquisition, AEs, health-care resource use and post-progression therapy. In the base-case analysis, list prices were used for initial targeted treatments and discounted prices available to English hospitals were applied to symptomatic and subsequent (after progression) treatment with octreotide. We also excluded subsequent treatment costs from the base-case analysis of GI and lung and GI (midgut) NETs and explored their likely importance in sensitivity analyses.

In the base-case analysis of pNETs, sunitinib produced the most life-years per patient at 6.39, followed by everolimus at 4.69 and BSC at 3.46. The expected discounted QALYs were 3.24, 2.51 and 1.91, respectively, and the respective discounted costs were £43,192, £42,646 and £15,761 respectively. Sunitinib (extendedly) dominated everolimus, that is, although both targeted treatments produced additional QALYs compared with BSC, sunitinib did so at a lower cost per QALY gained than everolimus and with a greater total number of

QALYs produced. At list prices, the ICER for everolimus compared with BSC was £45,493 per QALY and the ICER for sunitinib compared with BSC was £20,717 per QALY.

In the base-case analysis of GI and lung NETs, treatment with everolimus resulted in 6.21 life-years and 3.74 discounted QALYs per patient, whereas BSC yielded 4.82 life-years and 3.05 discounted QALYs per patient. The total per-patient discounted costs to the NHS for these two treatment options were £47,334 and £16,526 respectively. At list prices, the ICER was £44,557 per QALY gained for everolimus compared with BSC.

In the GI (midgut) population, in the base-case analysis, treatment with everolimus resulted in 7.50 life-years and 4.37 discounted QALYs per patient, whereas treatment with BSC resulted in 7.05 life-years and 4.19 discounted QALYs per patient. The total costs of these two treatment options were £55,842 and £21,119 respectively. Therefore, at list prices, the ICER was £199,233 per QALY for everolimus compared with BSC. This figure was highly uncertain because of the lack of midgut subgroup-specific OS data from RADIANT-4.

A range of scenario analyses were conducted. In pNETs, adjustment for the effect of crossover on OS had a large effect on cost-effectiveness. When relative effectiveness estimates from intention-to-treat OS data were used, treatment with everolimus resulted in higher costs and fewer QALYs than sunitinib and the ICER relative to BSC was £136,455 per QALY (compared with £45,493 in the base case), whereas the ICER for sunitinib compared with BSC was £37,217 per QALY (compared with £20,717 in the base case), at current list prices.

In the GI (midgut), applying background mortality produced ICERs for everolimus that were > £40,000 per QALY (compared with £199,000 in the base case). Another scenario involved the indirect comparison of everolimus and BSC with 177Lu-DOTATATE for GI (midgut) NETs. In analyses restricted to costs and benefits accrued up to disease progression, 177Lu-DOTATATE (extendedly) dominated everolimus (which had an ICER of £90,181 relative to BSC at list prices) and had an ICER of £30,115 relative to BSC.

End-of-life criteria

Based on the data from the three included trials (RADIANT-3, A6181111 and RADIANT-4), only sunitinib plus BSC in the pNETs population of A6181111 may meet the end-of-life criteria.

Conclusions

There is a high degree of uncertainty around the clinical effectiveness and cost-effectiveness of everolimus, 177Lu-DOTATATE and sunitinib in the treatment of advanced, progressive pNETs and GI and lung NETs. This uncertainty has its origins in the lack of data that naturally accompanies a rare condition. The evidence suggests that targeted initial treatments do provide benefits for PFS but the effects on OS are uncertain because of the immaturity of some of the OS data and because of substantial treatment switching by patients on disease progression in some trials.

Another area of uncertainty is the relative effects of targeted treatments on HRQoL. Although some of the trials underpinning this technology assessment review have measured this outcome, they tend to cover only the phase while patients are on treatment and it is therefore not known how HRQoL evolves over time or towards the end of life. Even while patients are on active targeted treatment, the available HRQoL data are inadequate to differentiate between treatments.

Seeking to address uncertainties in the evidence, we requested data from sponsors of the main trials; however, we obtained data that were outdated and that related to only one trial. Further valuable research would use individual patient data from RADIANT-4 to explore (1) the effect of adjustment for crossover from placebo to active treatment on OS and cost-effectiveness and (2) the robustness of the results of indirect comparisons with the NETTER-1 trial using methods ranging from simple Bucher-type methods to

more elaborate matching methods, such as those reviewed and investigated in this assessment. Similar analyses for pNETs using updated OS data are also warranted.

Nevertheless, in pancreatic NETs, at current list prices, the ICERs relative to BSC are likely to be about £20,000 per QALY for sunitinib and about £45,000 per QALY for everolimus. Everolimus is expected to have a similar ICER for GI and lung NETS, but is unlikely to be cost-effective for GI (midgut) NETs. The effectiveness evidence on 177Lu-DOTATATE is still too immature to make conclusive statements about cost-effectiveness, but our exploratory analyses suggest that it produces significantly better PFS outcomes than everolimus or BSC and, purely based on these outcomes, its ICER compared with BSC is approximately £35,000 per QALY.

Study registration

This study is registered as PROSPERO CRD42016041303.

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