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Systematic or Meta-analysis Studies

Chemotherapy for advanced non-pancreatic well-differentiated neuroendocrine tumours of the gastrointestinal tract, a systematic review and meta-analysis: A lost cause?

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ABSTRACT

Background: Chemotherapy is well-established in the treatment of patients with well-differentiated neuroendocrine tumours (NETs) arising from the pancreas (pNETs); however, its role in patients with gastrointestinal non-pancreatic NETs (non-pNETs) is uncertain. This systematic review assesses the evidence for the role of chemotherapy in well-differentiated non-pNET patients.
Methods: Eligible studies (identified using MEDLINE) were those reporting response and/or survival data for patients with well-differentiated non-pNETs receiving systemic chemotherapy. The primary end-point was overall-response (OR) rate; secondary end-points were progression-free survival (PFS), overall survival (OS), disease-stabilization (DS) and disease-control (DC) rates.
Results: Of 6434 studies screened, 20 were eligible: one randomised phase III trial, 2 randomised phase II studies, 10 single-arm phase II trials and 7 retrospective analyses including a total of 264 patients (median of 11 patients per study, range 6–49); and employing multiple chemotherapy schedules. The mean "median PFS" and "median OS" were 16.9 months (95%-confidence interval (CI) 3.8–30.04) and 32.2 months (95%-CI 10.4–54.2), respectively. The non-weighted mean OR, DS and DC rates were 11.5% (95%-CI 5.8–17.2), 56.5% (95%-CI 38.1–74.9) and 70.7% (95%-CI 54.9–86.5), respectively. In studies including both pNETs and non-pNET patients, meta-analysis showed a lower OR-rate in the non-pNET patients when compared to pNETs [odds ratio (OR) 0.35 (95% CI 0.18–0.66)]; however significance was lost when high-risk bias studies were excluded in a sensitivity analysis [OR 0.45 (95% CI 0.19–1.07); *p*-value 0.07].
Conclusion: Studies were of evidence level-C with heterogeneous populations and treatments; and small patient numbers. Well-designed, prospective studies are needed to adequately evaluate the role of chemotherapy in this setting.

Introduction

Neuroendocrine tumours (NETs) arise from neuroendocrine cells, which are widely distributed throughout the body; gastro-intestinal NETs (GI-NETs) are relatively rare, although the incidence has been rising in recent years [1].

Location of the primary tumour, stage at diagnosis, tumour grade and the ability to secrete hormones are the main factors involved in the selection of the treatment strategy and prognosis of GI-NETs.

Tumour grade is determined by tumour morphology, proliferation index (Ki-67 index) and mitotic count. World Health Organisation (WHO)/European Neuroendocrine Tumour Society (ENETS) guidelines divide GI-NETs into two main groups: well-differentiated NETs [subdivided into grade 1 (low grade: Ki-67 index ⩽2% or mitotic count ⩽1) and grade 2 (intermediate grade: Ki-67 index 3–20% or mitotic count 2–20) tumours] and poorly differentiated NETs [high grade: grade 3: Ki-67 index >20% or mitotic count >20] [2,3].

Gastrointestinal NETs can also be classified according to their origin in two main groups: pancreatic NETs (pNETs) and non-pancreatic NETs (non-pNETs). Overall, most NETs are

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non-functional; however, non-pNETs (especially those arising from the small bowel), are more-frequently functional (e.g. by secretion of serotonin causing the carcinoid syndrome) than pNETs [4].

Surgical resection is the cornerstone of treatment for patients with localised disease; in contrast, patients diagnosed with advanced-stage disease are often beyond curative surgery, and are managed with palliative intent.

For patients with advanced poorly-differentiated NETs, treatment usually consists of systemic chemotherapy (e.g. platinum and etoposide combination), regardless of tumour origin [5]. The prognosis is poor; usually less than one year. This patient group will not be discussed further in this review.

Patients diagnosed with advanced well-differentiated GI-NETs have an estimated median overall survival between 2 and 5 years depending on the series [1]. For appropriate management, a treatment strategy needs to be planned according to patient and tumour characteristics.

A feature of NETs is the expression of somatostatin receptors; therefore treatment with *somatostatin analogues* (SSAs) such as octreotide and lanreotide has been used widely for both symptom control and with anti-proliferative intent. Their anti-tumour efficacy has been shown in randomised phase III studies [6,7].

Based on the same rationale, targeted radiotherapy using radiolabelled SSA (*peptide receptor radionuclide therapy* [PRRT]) can be used for patients with avid tracer uptake on octreotide scan. The most frequently used radionuclides are yttrium (^{90}Y) and lutetium (^{177}Lu) [8,9]. The recently-presented NETTER-1 clinical trial [ClinicalTrials.gov identifier: NCT01578239] in patients with progressive well-differentiated mid-gut NETs is the first confirmation of benefit (improved progression-free survival [PFS]) in a prospective randomised clinical trial [10].

Interferon (IFN) has the ability to stimulate T-cell function, controlling the secretion of tumour products. Moreover, it has also been suggested to inhibit tumour growth by activation of the T-cell response against the tumour and inhibition of angiogenesis. Therefore, IFN has been used and tested in many retrospective and small prospective studies showing reduction of symptoms related to hormone secretion in 40–50% of patients with a partial-response rate of around 10% [11]. However, it is not widely used due to lack of prospective quality evidence.

Development of *targeted therapies* has changed the management of GI-NETs. Two phase III trials (one with everolimus [12] and one with sunitinib [13]) demonstrated a significant improvement in PFS leading to licensing and regulatory approval for patients with advanced progressive p-NETs. In contrast, the benefit of everolimus and sunitinib in non-pNETs is not well established; the RADIANT-2 phase III trial showed no clear benefit for everolimus in patients with functional non-pNET [14]. The RADIANT-4 trial, recently presented in abstract form, has shown an improved PFS in patients with non-pancreatic, non-functional gastrointestinal NETs compared to placebo (ClinicalTrials.gov identifier: NCT01524783) [15]; this is yet to be licensed for this indication.

In selected cases, predominantly in patients with high tumour burden, classical cytotoxic *chemotherapy* can be considered for the treatment of patients with well-differentiated NETs [16]. Currently, no standard chemotherapy schedule is available and the selection of treatment is based on comorbidities and/or toxicity profile. Alkylating agents (such as streptozocin, temozolomide and dacarbazine) alone or in combination with 5-fluorouracil (5-FU) or capecitabine (5-FU pro-drug) are widely used [17–24].

While many options for treatment are available for patients with pNETs, only SSAs are currently licensed for the treatment of patients with non-pNETs. Currently, systemic options for treatment are limited to SSAs (based on Level B1 evidence); IFN (based on Level C evidence) or PRRT (based on Level C evidence, pending publication of the results from the NETTER-1 randomised phase III study). In addition, published results of the recent RADIANT-4 study may allow everolimus to emerge as a new treatment option.

Chemotherapy has been shown to be active in patients with pNETs [17,19,25], mainly due to higher response-rates reported; in addition some studies have shown significant responses in the non-pNET population [26,27]. Unfortunately, due to limitations of cross-trial comparison, differences in chemotherapy efficacy between these two populations remain unclear. This systematic review assesses the available data relating to chemotherapy in patients with well-differentiated non-pNETs. A meta-analysis of selected studies reporting outcome data for chemotherapy in both pNET and non-pNET patients was also performed to contextualise results across the disease groups.

Materials and methods

Participants, interventions and eligible studies

This systematic review focused on studies including patients with advanced (locally advanced, recurrent or metastatic) well-differentiated (WHO grade 1 and grade 2) non-pancreatic gastrointestinal NETs treated with systemic chemotherapy. Studies with patients treated with adjuvant chemotherapy were not eligible.

Eligible interventions included any systemic chemotherapy regimen given with palliative intent; studies were excluded if no systemic chemotherapy was given or if systemic chemotherapy was used in combination with PRRT or local therapies such as radiotherapy, liver embolisation or chemoembolisation, surgery or photodynamic therapies. Studies exploring the role of other therapies such as PRRT, targeted therapies or SSA or IFN alone were considered ineligible.

In addition, studies were required to report response and/or survival data for the cohort of non-pNET patients in order to be eligible for the descriptive analysis; studies were excluded if the reported response assessment included clinical or biochemical responses (i.e. only radiological responses were included). In those studies in which response data for the non-pNET cohort was available, collection of radiological response for patients with p-NETs was performed for comparison (meta-analysis). Meta-analyses, systematic reviews, clinical trials and retrospective analysis were eligible; case reports or small case series (less than 5 patients) were excluded. If insufficient clarification regarding grade of differentiation and/or if results were given for a population of mixed poorly-differentiated and well-differentiated NETs, or mixed non-pNET and other NETs, studies were excluded, as were phase I clinical trials with no data available for response/survival.

Search strategy

This systematic review, registered in the PROSPERO database [registration number CRD42015024886 [28]], was undertaken using the MEDLINE database [29]. A search was performed (updated on 6th August 2015) to identify eligible studies; no dates of publication or language limits were applied. MEDLINE searches were performed as follows:

- Search strategy 1: "gastrointestinal neoplasms"[MeSH Terms] AND ("drug therapy"[MeSH Terms] AND ("carcinoma, neuroendocrine"[MeSH Terms] OR "neuroendocrine tumours"[MeSH Terms] OR "endocrine gland neoplasms"[MeSH Terms])) NOT review[Publication Type].
- Search strategy 2: (("neurosecretory systems"[MeSH Terms] OR ("neurosecretory"[All Fields] AND "systems"[All Fields]) OR "neurosecretory systems"[All Fields] OR "neuroendocrine"[All Fields]) AND ("carcinoid tumour"[MeSH Terms] OR ("carcinoid"[All Fields] AND "tumour"[All Fields]) OR "carcinoid