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Chemotherapy for Gastro-Enteropancreatic Endocrine Tumours

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Gastro-enteropancreatic endocrine tumours · Chemotherapy · Well-differentiated tumours · Poorly differentiated tumours

Abstract
Despite similar histological and morphological aspects, gastro-enteropancreatic (GEP) endocrine tumours represent a heterogeneous group of tumours with varying clinical expression depending on tumour type (functional or not), origin and extension, but also on histological differentiation and proliferative capacity. The natural history of well-differentiated tumours is often favourable without treatment and GEP endocrine tumours may remain indolent for many years. Chemotherapy may however be indicated in the presence of symptomatic non-progressive disease (progression evaluated over 3–6 months). In contrast, poorly differentiated GEP endocrine tumours are frequently aggressive and early treatment is required. Accurate staging is mandatory and where surgery is possible (even in the event of limited metastatic disease), this option should be re-evaluated in a multidisciplinary approach. Approximately 2/3 of malignant GEP tumours are metastatic at discovery and surgery is possible in a minority of patients; therefore, chemotherapy, with/without other strategies (e.g. local ablation), is frequently indicated in patients with symptomatic, bulky or progressive disease. For well-differentiated pancreatic tumours, the reference association is Adriamycin with streptozotocin yielding objective responses (OR) in 40–60% of patients. Prolonged treatment is limited due to potential cardiotoxicity of Adriamycin and standard 2nd-line regimens are not of proven efficacy; thus, other treatment modalities are usually additionally required (e.g. chemo-embolisation). A significant OR may render a small number of patients secondarily amenable to surgery. Published series evaluating chemotherapy for midgut endocrine tumours are outdated and disappointing. Objective response rates with combined associations (including either 5-fluorouracil and/or streptozotocin) rarely exceed 20% and where possible, chemo-embolisation for hepatic metastases combined with somatostatin analogues (± interferon) should be preferred. Poorly differentiated GEP tumours are generally aggressive tumours with metastases at diagnosis and tend to progress rapidly. Surgery is rarely possible and ineffective even in locally advanced disease due to a high risk of recurrence. Chemotherapy, using cisplatin and etoposide, is the reference treatment and frequently yields OR rates >50%. However, despite being chemosensitive, disease control is limited (8–10 months). Overall, advances in therapeutic chemotherapeutic options are required in the management of all types of advanced

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GEP endocrine tumours and evaluation of new drugs (e.g. irinotecan) and combination strategies (chemotherapy with local ablative therapies) are required in the future.

Introduction

Endocrine tumours of gastro-enteropancreatic (GEP) origin are a heterogeneous group of tumours of variable prognosis. The natural history varies from a frequently indolent course for tumours which are well differentiated to a much more aggressive form with poorly differentiated tumours. The principles of management of patients with GEP endocrine tumours depend on a number of factors requiring a multidisciplinary approach. Recent advances in surgery imply that patients even with bilobar liver metastases may be deemed suitable to surgery using two-stage hepatectomies [1, 2] and therefore prior to considering patients for chemotherapy, a surgical option should always be reconsidered. Nonetheless, surgery is rarely possible in patients with metastatic disease and other approaches are therefore necessary.

As opposed to treatment decisions for other solid tumours of the digestive tract, 'wait-and-see' strategies can often be adopted in patients with GEP tumours. The slow-growing nature of well-differentiated tumours means that chemotherapy and other treatment strategies should be reserved for patients with progressive disease. Indeed, to date interpretation of data on treatment of patients with GEP tumours has been hampered by the lack of evidence for progressive disease in a number of studies. Documented progression (on either solid clinical grounds or a $\geq 25\%$ increase in targeted lesions or appearance of a new disease in patients with non-symptomatic disease) should be based on accurate and comparable evaluation of clinical, biological and morphological data at least at 3-monthly intervals. Given that response to cytotoxic agents in patients with GEP tumours may be short-lived, determining the correct moment to commence treatment is often difficult. Early treatment at the outset is, on the contrary, usually necessary for patients with aggressive well-differentiated tumours and for those with poorly differentiated lesions whose natural history mirrors that of small cell lung cancer. Another consideration in commencing treatment at the moment of diagnosis is the presence of bulky disease, especially the presence of extensive liver metastases (usually $>70\%$).

Until now, the type of chemotherapy has been largely based on the site of origin of the primary tumour and on the histological differentiation. Endocrine tumours of the duodenum or pancreas, whether functional or not, are considered for cytotoxic regimens, which greatly differ from those of midgut origin. In addition, given that tumour differentiation also dictates response to individual cytotoxic protocols, correct histological classification should be applied using strict WHO criteria [3]. Accurate histological classification is not always easy as interobserver differences among pathologists are not uncommon and guidelines to increase uniformity are required. The importance of accurate histology cannot be underestimated and in cases where doubt exists, slides should be sent for an expert opinion. The recent use of the proliferation index Ki-67 has been helpful in distinguishing certain tumours and guiding treatment regimens; this marker is invariably high ($>15\%$) in poorly differentiated lesions; however, cases with a histological architecture resembling well-differentiated tumours and moderately elevated Ki-67 (between 2 and 15% or 'borderline tumours') [3] may be problematic when it comes to choosing chemotherapy. The appraisal of proliferation indices on treatment outcomes is requisite in future protocols.

Chemotherapy for Well-Differentiated GEP Tumours of the Pancreas or Duodenum

Apart from insulinomas, other GEP tumours from the pancreas or duodenum are frequently associated with metastatic disease and curative surgical options are rarely possible ($<25\%$) [4]. Thus, cytotoxic therapy is a frequently posed question in these patients. Single-agent chemotherapy with streptozotocin yielded tumour response rates of between 36 and 42% [5, 6]; however, these early studies can be criticized with respect to the crude methods of interpreting morphological responses. Other monotherapies including chlorozotocin, doxorubicin, 5-fluorouracil (5-FU) [7] or dacarbazine [5, 8] have been used but criticised either due to the high toxicity rate or lack of objective response. Such strategies have been universally replaced by combination chemotherapy protocols. As seen in table 1, many associations have been used with streptozotocin, 5-FU and anthracyclines forming the cornerstone of the regimens tested. The results by Moertel et al. [9] in 1992 using streptozotocin and doxorubicin have not been bettered to date, with a 69% objective response rate and a median survival of 26 months; this compared to a 45% objective response rate for 5-FU and streptozotocin. The

Table 1. Combination chemotherapy for well-differentiated endocrine tumours of the pancreas and duodenum

Reference	Phase	Regimen	n	Objective response %	Response duration months	Median survival months
Moertel et al. [10]	III	STZ	42	36	17	17
		STZ +5-FU	42	63	17	26
Moertel et al. [9]	III	DOX + STZ	36	69	18	26
		5-FU + STZ	33	45	14	18
Eriksson et al. [13]	II	DOX + STZ	25	36	22	–
Bukowski et al. [14]	II	CLZ +5-FU	44	36	11	–
Rivera and Ajani [11]	II	STZ +5-FU + DOX	12	55	15	21
Cheng and Saltz [15]	II	DOX + STZ	16	6	18	–
Bajetta et al. [37]	II	5-FU + EPI + DTIC	15	27	10	–

STZ = Streptozotocin; DOX = doxorubicin; CLZ = chlorozotocin; EPI = epirubicin; DTIC = dacarbazine.

same group had previously obtained better results with 5-FU/streptozotocin in a phase III trial comparison to monotherapy with streptozotocin [10]. While no group has managed to achieve the same response rates, objective response rates of between 36 and 55% have been established using streptozotocin/doxorubicin [11–14] with the exception of Cheng et al. [15] who reported a 6% response rate in a group of 16 patients. Cheng et al. [15] in their article questioned the reliability of the earlier studies by Moertel et al. [9] especially concerning methods of measuring responses. However, a recent report by Delaunoit et al. [12] in 45 patients found a 36% overall response rate using well-defined criteria for recruitment and evaluation; in addition, 2- and 3-year overall survival rates were 50 and 24%, respectively. Such discrepancies are difficult to explain; however, while the 69% response rates by Moertel's group have not been re-achieved, a combination of streptozotocin with either doxorubicin or 5-FU in the treatment of advanced GEP tumours of the pancreas or duodenum is supported by recent data [11–14]. Nonetheless, despite being the standard treatment, newer agents need to be tested in appropriate phase II and III trials.

The cumulative cardiotoxicity of doxorubicin, quickly attained following the standard Moertel regimen (the prevalence of cardiomyopathy increases significantly when patients are given doses of doxorubicin >550 mg/m^2 [16]) means that strategies with 5-FU should be considered either at the outset or following maximal treatment with anthracyclines. The use of agents with less cardiotoxicity may also be worthwhile (e.g. epiadriamycin and liposomal formulations [17, 18]); however, appraisal of both efficacy and toxicity is required prior to universal approval for this indication. Careful monitoring of renal function with 24-hour proteinuria prior to each cycle administration of streptozotocin is advised to avoid permanent renal damage. Nausea and vomiting are usually not problematic provided adequate antiemetics are systematically administered (we combine 5-HT$_3$ inhibitors with corticosteroids on a routine basis unless otherwise contra-indicated).

Well-Differentiated GEP Tumours of Midgut Origin

Similar to well-differentiated GEP tumours of the pancreas and duodenum, in GEP tumours of midgut origin, single-agent regimens have been largely disappointing with objective response rates <25% and response durations rarely exceeding 3 months [5]. In 1979, Moertel and Hanley [19] combined 5-FU with streptozotocin in midgut carcinoids yielding a response rate of 33%. Studies using the same combination since then have failed to reproduce these results (table 2) [20–23]. Therefore, other combinations have also been examined and apart from a 40% objective response rate for patients with midgut carcinoids observed using doxorubicin and streptozotocin in a phase II study [24], no other reliable cytotoxic regimen has been found for patients with advanced or metastatic disease of midgut origin. The association of cytotoxics with interferon has also been investigated with largely poor outcome success apart from one study by Andreyev et al. [25] who demonstrated a 47% objective response using a combination of interferon with continuous infusion of 5-FU; response duration lasted 21 months. The excellent, and reproducible, results obtained with chemo-

Table 2. Combination chemotherapy for well-differentiated GEP tumours of midgut origin

Reference	Phase	Regimen	n	Objective response %	Median survival months
Moertel and Hanley [19]	III	5-FU + cyclophosphamide	47	26	–
		5-FU + STZ	422	33	–
Engstrom et al. [20]	III	5-FU + STZ	80	22	15
		DOX	81	21	11
Moertel et al. [21]	III	MTX + cyclophospahmide	16	0	–
		STZ + cyclophosphamide	14	0	–
Frame et al. [24]	II	DOX + STZ	33	40	11
Moertel et al. [22]	II	VP16 + cisplatin	13	0	–
Di Bartolomeo et al. [23]	II	5-FU + DOX + DTIC	20	10	5

STZ = Streptozotocin; DOX = doxorubicin; DTIC = dacarbazine.

Table 3. Combination chemotherapy for poorly differentiated GEP tumours

Reference	Regimen	n	Objective response %	Duration of response months	Median survival months
Moertel et al. [22]	etoposide + cisplatin	18	67	8	19
Seitz et al. [28]	etoposide + cisplatin	11	54	–	–[1]
Mitry et al. [29]	etoposide + cisplatin	41	42	9	15

[1] 65% survival at 1 year.

embolisation in patients with hepatic metastases and carcinoid syndrome (tumour response rates of approximately 40–50% and excellent control of symptoms) [26] argue for its use in such patients with liver metastases. In patients with extensive disease outside of the liver (e.g. carcinomatosis or bony metastases), current treatment strategies are wanting and novel approaches using peptide receptor radionuclide therapy [27] have appeared more seductive to date than endless trials with largely ineffective cytotoxics. Investigation of newer treatment options such as targeted molecular approaches may also prove of value in these patients.

Chemotherapy of Poorly Differentiated GEP Tumours

Standard treatment in patients with advanced poorly differentiated GEP tumours has largely been based on protocols containing etoposide and cisplatin (table 3). While tumour response rates are often good (42–65%), duration of response rarely exceeds 10 months and median survival is in the order of 15 months [22, 28, 29]. Newer options are required for the treatment of these patients.

Other Indications for Chemotherapy in GEP Tumours (Adjuvant or Neo-Adjuvant)

To date, there have been no data to support the systematic use of chemotherapy in an adjuvant setting. Some units have adopted policies of 4 cycles of adjuvant chemotherapy following resection of hepatic metastases (including some unpublished personal observations); however, evaluation of such treatment requires a randomized study comparing adjuvant treatment to surgery alone. Adjuvant chemotherapy is frequently employed following hepatic transplantation for metastases of digestive GEP tumours [2, 30]; however, its indication has not been evaluated and such a study would prove very difficult given the rarity of transplantation in this setting. While chemotherapy in a neo-adjuvant setting has not been formally evaluated in patients with digestive GEP tumours, we and others have

performed resection of both primary tumours and liver metastases following excellent chemotherapy-induced objective responses (personal experience). A surgical approach should be discussed where chemotherapy or other strategies render patients (event with metastatic disease) operable.

Perspectives

Agents showing promising results in the setting of other solid gastro-intestinal tumours have been applied to patients with GEP tumours. Irinotecan, in a single-agent form, has recently been found to be inactive in patients with carcinoid syndrome [31]. Paclitaxel in high dose (250 mg/m^2) was also found to be disappointing with an 8% response rate and significant haematological toxicity [32]. A search for expression of tyrosine kinase receptors, namely c-kit, has also been performed in GEP tumours. Fjällskog et al. [33] found 35 of 38 tissue specimens (92%) from GEP tumours to express c-kit on tumour cells. However, a phase II trial using the PDGF-R inhibitor imatinib (found to be revolutionary in gastro-intestinal stromal tumours) in 21 patients with advanced GEP tumours demonstrated only weak biological activity with a partial response in only 1 patient; 8 patients with progressive disease at study entry were progression-free at 3 months [34]. This might be explained by the mixed results for c-kit staining found in GEP tumours as highlighted by Theodossiou et al. [35] who found only 9% positive weak staining in 21 patients with metastatic GEP tumours. Interestingly, inhibitors of epidermal growth factor receptors have shown antiproliferative activity in in vitro GEP tumour models. Hopfner et al. [36] demonstrated a time- and dose-dependant growth inhibition of the insulinoma cell line as well as in pancreatic BON cells and in gut SCT-1 cells. Discerning antiproliferative mechanisms should provide more efficacious chemotherapeutics and molecular arsenals for the targeting of these tumours. One such approach which should work stems from the vascularity of such tumours allowing the intriguing prospect of developing anti-angiogenic agents (e.g. anti-VEGF factors and inhibitors of EGF-R) and while industry-driven research is mainly focused on other digestive solid tumours, advances in the latter area will no doubt aid in our approach to GEP tumours.

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