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Review

Chemotherapy and biotherapy in the treatment of neuroendocrine tumours

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Summary

The medical treatment of neuroendocrine GEP tumours must be based on the growth properties of the tumour. Medical treatment includes chemotherapy, somatostatin analogues and alpha interferons. Chemotherapy has been particularly active in patients with high proliferating neuroendocrine tumours such as endocrine pancreatic tumours and lung carcinoids. Streptozotocin-based combinations including 5-flourouracil and doxorubicin have generated partial remissions in 40%–60% of the patients giving a median survival of about two years in patients with advanced disease. Cisplatinum plus etoposide have demonstrated significant antitumour effects in anaplastic endocrine pancreatic tumours and lung carcinoids. However, in low proliferating tumours such as classical midgut carcinoids the response rates with the same combinations of cytotoxic agents have only generated short lasting responses in less than 10% of patients. In these patients, biological treatment has been of benefit. Alpha interferon at doses of 3–9 million units three to seven times per week subcutaneously, has given biochemical response rates of 50% and significant tumour reduction in about 15% of patients with long duration, up to three years.

Somatostatin analogues have been widely used in the treatment of neuroendocrine gut and pancreatic tumours. The currently available somatostatin analogues particularly bind somatostatin receptor 2 and 5 and with low affinity also receptor subtype 3. Octreotide is registered in most countries for the treatment of patients with carcinoid syndrome and also VIP and glucagon producing tumours. Regular octreotide at standard doses of 100–300 μg/day gives symptomatic responses in a medium of 60% of patients and biochemical responses in up to 70% of patients. Significant tumour responses are rare, less than 5%. Long-acting formulations of somatostatin analogues have been of significant benefit for the patients with similar response rates as for regular formulations. The quality of life has been significantly improved by using the long-acting formulations.

Key words: alpha interferon, lanreotide, octreotide, somatostatin analogues, streptozotocin

Introduction

The medical treatment of neuroendocrine GEP tumours must be based on the growth properties of the tumour. Medical treatment includes chemotherapy, somatostatin analogues and alpha interferons. Because of the rarity of these tumours, clinical studies have frequently been reported in a very tenious fashion. Furthermore, many of the studies do not take into account differencies in biological behaviour between classical midgut carcinoids and endocrine pancreatic tumours. In addition, many clinicians are still reluctant to treat patients with neuroendocrine GEP tumours without clinical symptoms since they have been assigned a good prognosis. However, a critical look at the survival data in patients with malignant neuroendocrine GEP-tumours showed a five-year survival rate of 20% and and average survival of two years when liver metastases are present in carcinoid tumour patients. For endocrine pancreatic tumours, the survival data are even worse [1, 2]. Today there is no medical treatment for 'bulky' disease that cures the patient. However, the quality of life for patients with functioning tumours has been significantly improved by the introduction of biological treatment, in particular somatostatin analogues and alpha interferons.

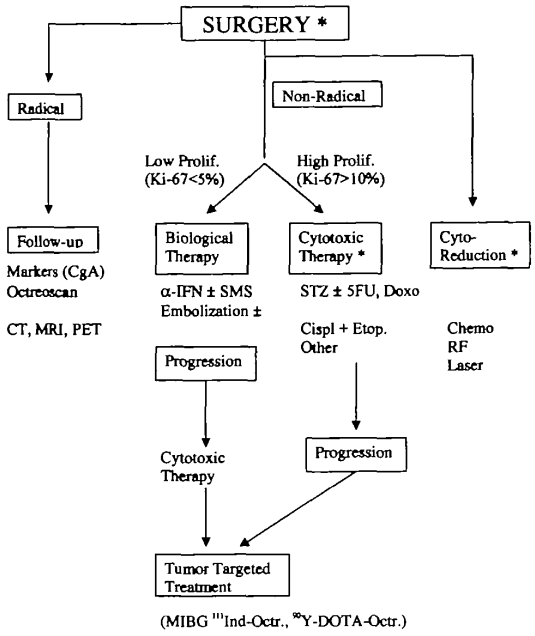
Chemotherapy

Chemotherapy has been considered 'the gold standard' for treatment of most GEP tumours. However, it has usually been reported in studies involving a limited numbers of patients with variable criteria for assessing antitumour responses. Chemotherapy for endocrine pancreatic tumours has been of significant benefit [3–5]. Streptozotocin based combinations including 5-flourouracil (5-FU) and doxorubicin have generated partial remissions in 40%–60% of the patients, giving a median survival of about two years in patients with metastatic disease. In contrast to the experience of chemotherapy for endocrine pancreatic tumours, classical midgut carcinoids have been rather resistant to various combinations of chemotherapeutic drugs. Combination chemotherapy trials, including streptozotocin, 5-FU, cyclophosphamide or doxorubicin has only generated short-lasting responses in fewer than 10% of the patients [2, 5, 6].

However, in a subset of carcinoid tumours in particular forgut (lung, thymic), cytotoxic agents have produced remarkable remissions, in particular a combination of cisplatinum and etoposide. That is also true for anaplastic endocrine pancreatic tumours but not for highly differentiated tumours [8].

Liver targeted chemotherapy has been reported in some trials where objective responsed have been noticed in 60% of the patients with a median duration of 18 months, in patients receiving embolization + DTIC + doxorubicin + 5-FU + streptozotocin [9]. Other trials including embolization + doxorubicin have generated response rates between 35%–78% with a duration of 17–24 months with significantly lower side-effects.

Today, chemotherapy should be primarily reserved for patients with high proliferation capacity irrespective of the localisation of the primary tumour (see algorithm, Figure 1). The precise level of the proliferation index (Ki-67) has not been determined but definitely proliferation indices of about 10% and wide spread disease might support systemic chemotherapy as a first line [10, 11].



* NB! SMS could be used during surgery and cytoreduction to facilitate the procedure. Can also be used in combination with cytotoxic therapy.

Figure 1. Neuroendocrine tumors.

Biotherapy

Biological treatment of neuroendocrine tumours include alpha interferons and somatostatin analogues.

Interferon

Alpha interferon was introduced by our group in the treatment of carcinoid tumours in 1982, because of its ability to stimulate natural killer cell function and to control hormone secretion, clinical symptoms and tumour growth [12]. Since then, more than 400 patients have been reported in the literature treated with alpha interferon [13–16]. Today recombinant alpha interferon are used (Intron, α-interferon 2b and Roferon, α-interferon 2a). Alpha interferon 2b is the most commonly used α-interferon. The applied doses of α-interferon have been 3–9 MU 3–7 times/week subcutaneously. The dose has to be individually titrated in the patients and as a guide-line the leukocyte count should be reduced to 3.0 $\times 10^9$/l. By using such titration the biochemical response rate in carcinoid tumour has been reported to be 50% and significant tumour reduction 15%. The median duration response has been 32 months and 35% of the patients showed stabilisation of their disease with no further tumour growth. Only 15% of the patients continued to progress. Survival data from our own center and from others, showed improved survival after treatment with α-interferon in malignant classical midgut tumours with a carcinoid syndrome. The median survival for patients with malignant carcinoids and liver metastases is at our institution more than eight years during continuous biotherapy [17]. Also in patients with low proliferating endocrine pancreatic tumours, a response rate of about 50% have been obtained lasting for more than two years. The mechanism of action of α-interferon is supposed to be a direct effect on the tumour cells but also trigging the immune system. It is known to inhibit the cell cycle in G-1 to S-phase in carcinoid tumour cell and it inhibits the production of growth factor/receptors and other agents secreted by tumour cells. It is also known to induce class 1 antigens on the cell surface and thereby attract various response cells of the immune system. It is also assumed that α-interferon has an anti-angiogenetic effect, which has been explored in children treated for multiple hemangiomas.

Alpha interferon has been combined with somatostatin analogues, especially octreotide, with significant potentiation of the clinical effect.

In a group of patients resistant to somatostatin analogues, the addition of α-interferon (median 5 MU three times/week) generated biochemical responses in 77% of the patients with 18% complete biochemical remission [18]. However, no significant tumour reduction was seen in this trial. Theoretical basis for using the combination of these two compounds is based on studies *in vitro* and *in vivo* in BON-cells, which are neuroendocrine differentiated cells. The combination of octreotide and α-interferon causes a significant growth inhibition compared to a single agent. Another recent study from our own group in malignant endocrine pancreatic tumour resistant to either α-interferon alone, somatostatin analogue alone or cytotoxic treatment, has generated 35% objective tumour reduction and 50% biochemical re-

sponses. These data are further supported by a recent publication from a German group, showing tumour reduction in more than 50% of patients receiving the combination of α-interferon and somatostatin analogue [19]. The adverse effects of α-interferon treatment include mainly flu-like symptoms for the initial 3–4 days, which can be managed by paracetamol or aspirin. More severe adverse reaction is the chronic fatigue syndrome which occur in about 50% of the patients and sometimes also give mental depression. Another adverse reaction might be induction of autoimmune phenomenon with development of anti-nuclear, thyroid antibodies and sometimes development of thyroid dysfunction. Also neutralising antibodies to recombinant α-interferon might develop to which might abrogate the antitumour response.

Interferon should be used in low proliferating tumours with limited tumour burden such as classical midgut carcinoids, where it has shown an antiproliferative effect (Figure 1). In the future, trials of adjuvant treatment after surgery with curative intent should be done to explore whether α-interferon can prevent the development of metastatic disease later on.

Somatostatin analogues

Somatostatin analogues have been widely used in the treatment of neuroendocrine gut- and pancreatic tumours. They can inhibit the release of peptides from the tumours and by that improving the clinical symptoms related to these tumours. The currently available somatostatin analogues are particularly seeing somatostatin receptor 2 and 5, and with low affinity also receptor type 3 [20]. Octreotide is registered in most countries for the treatment of patients with carcinoid syndrome and also VIP and glucagon producing tumours. Today a large number of patients (more than a thousand) have been treated with somatostatin analogues. Regular octreotide at standard doses of 100–300 μg/day, give symptomatic responses in a median 60% of the patients [21]. Biochemical responses have been obtained in 70% of the patients and tumour responses in about 5%. When giving high-dose treatment (>3000 μg/day), the symptomatic and biochemical responses are similar but the tumour responses are slightly increased to 11% [22]. Recently a slow release formulation has been developed for octreotide, Sandostatin-LAR, and the patients switch from regular octreotide to LAR at doses of 20–30 mg intramuscular per month, showing continuing biochemical response in more than 80% of the patients. Similar data has been obtained for a long-acting formulation of somatuline (lanreotide-PR) given 30 mg every two weeks intramuscular, where 50% of the patients showed biochemical response and a mean of 3% tumour responses. More interesting was the quality of life evaluation using QLQ-30, where a significant improvement in the quality of life was obtained during treatment with a long-acting formulation [23].

The average survival for patients with malignant midgut carcinoids has been estimated at 36 months for somatostatin analogue treatment. The side-effects of octreotide treatment are generally mild and include fat malobsorption and sometimes gall bladder dysfunction and gall stones. The long-acting formulation is a real advantage for patients just taking one injection every three to four weeks, instead of three times/day.

Somatostatin analogues will be the gold standard for management of hormonal clinical symptoms related to neuroendocrine GEP tumours for many years. Since there are five subtypes of somatostatin receptors, subtype specific analogues might resolve the precise single transduction pathway and action from each subtype of receptor. It has also been recently shown that there is a cross-talk between somatostatin receptors within the same cell which can modulate response to a certain subtype of somatostatin analogue.

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