Treatment of medullary thyroid carcinoma: an update

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Abstract

Prognosis and treatment effectiveness of medullary thyroid carcinoma (MTC) are largely related to the tumour stage, so that early diagnosis represents an important goal for the management of patients. Recent advances in genetic testing have improved the clinical approach to the familial MTC syndromes. There is general agreement that the primary operation for MTC should obtain the complete removal of the neoplastic tissue in the neck, because any adjuvant treatment has never been proven to be effective. The management of residual/recurrent or metastatic MTC still remains controversial, although a multimodal approach to advanced disease may be of value in palliation or local control of tumour progression. The role of surgery, external radiotherapy, radionuclide therapy and medical treatment, including biological response modifiers and cytotoxic drugs, are reviewed and discussed.

Introduction

Medullary thyroid carcinoma (MTC) was first recognised as a distinct clinical and pathological entity by Hazard et al. (1959). Since then, a number of landmark discoveries have increasingly improved our knowledge regarding the particular biology and clinical behaviour of this tumour.

MTC originates from the parafollicular C cells and accounts for about 5–10% of all thyroid cancers, both sexes being affected, with mild excess for females; the tumour can be sporadic in about 70–75% of cases or familial in the remaining 25–30% (Saad et al. 1984, Raue 1998, Kebebew et al. 2000). Sporadic MTC usually occurs as a unifocal clonal population of tumour cells, while the heritable forms are typically multifocal (Hazard 1977). Familial MTC is inherited as an autosomal dominant trait linked to chromosome 10, and may occur in three distinct clinical settings: as multiple endocrine neoplasia (MEN) 2A, as MEN 2B, or as familial MTC-only syndrome (FMTC) (Sipple 1961, Williams 1965, Giuffrida & Gharib 1998). The clinical features of the familial syndromes are listed in Table 1. Hereditary germline mutations of the RET proto-oncogene have also been found in sporadic MTC, and may be useful markers for nonhereditary disease (Romei et al. 1996). As a consequence of the recent advances in genetic technology, the application of RET proto-oncogene mutation analysis to the clinical management of hereditary MTC has simplified and enhanced the power of familial screening (Marsh et al. 1995, Wohllk et al. 1996).

C-cell hyperplasia in surrounding tumour tissue is a common finding in familial MTC; it is thought to progress towards nodular hyperplasia, eventually leading to malignancy through clonal progression (Wolfe et al. 1973, Hazard 1977). MTC synthesises and secretes large amounts of calcitonin (CT) and a number of other substances (Cobin 1992, Van Heerden & Hay 1994, Marsh et al. 1995, Giuffrida & Gharib 1998) such as calcitonin gene-related peptide (CGRP), carinoembryonic antigen (CEA), neuron-specific enolase (NSE), chromogranin-A, and adrenocorticotrophic hormone (ACTH) (Table 2).

Calcitonin is the most specific circulating and immunohistochemical marker for MTC, widely employed for diagnostic purposes (Tashjian et al. 1970, Giuffrida & Gharib 1998, Engleback et al. 2000). Calcitonin increased in all the cases of clinically palpable MTC; however, in smaller tumours and C-cells hyperplasia, basal levels may be normal, and only stimulated CT levels will confirm the diagnosis. Pentagastrin is a provocative agent for CT secretion, widely used for identifying both subclinical MTC, and gene carriers...
Table 1 Clinical features of familial medullary carcinoma syndromes.

<table>
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<tr>
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<th>Familial non-MEN MTC</th>
<th>MEN 2A</th>
<th>MEN 2B</th>
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<td>Multicentricity, bilaterality</td>
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<td>Multicentricity, bilaterality 100%</td>
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<td>C-cell hyperplasia 100%</td>
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<td>Pheochromocytoma (bilateral in 50% of cases)</td>
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<td>Mucosal neuromas of lips, eyes, tongue, gastrointestinal tract</td>
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<td>Rare</td>
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<td>Hirschsprung’s disease</td>
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Table 2 Secretory products of medullary thyroid carcinoma.

<table>
<thead>
<tr>
<th>Hormones and pro-hormones</th>
<th>Enzymes</th>
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<tr>
<td>Calcitonin</td>
<td>Neuron-specific enolase</td>
<td>Carinoembryonic antigen</td>
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<td>Calcitonin gene-related peptide</td>
<td>Histaminase</td>
<td>Chromogranin A</td>
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<tr>
<td>Katacalcin</td>
<td>DOPA-decarboxylase</td>
<td>Nerve growth factor</td>
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<td>ACTH</td>
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<td>Synaptophysin</td>
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<td>β-Endorphin</td>
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<td>β-Melanocyte stimulating hormone</td>
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<td>Somatostatin</td>
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<td>Neurotensin</td>
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<td>Serotonin</td>
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<td>Substance P</td>
<td>Corticotropin releasing hormone</td>
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<td>Vasoactive intestinal peptide</td>
<td>Bombesin</td>
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<td>Gastric-releasing peptide</td>
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in families at risk (Gagel et al. 1988, Ponder et al. 1988); the combined calcium and pentagastrin infusion test has been proposed in order to potentiate the secretagogue stimulus for calcitonin (Hennessy et al. 1974). In recent years, genetic screening has been progressively replacing biochemical tests (Barbot et al. 1994, Wohllk et al. 1996).

Usually, patients present a painless nodular thyroid enlargement, often accompanied by cervical adenopathies. Symptoms of ectopic hormone production are diarrhoea, facial flushing and, uncommonly, Cushing’s syndrome (Cobin 1992, Mure et al. 1995, Giuffrida & Gharib 1998). The correct diagnosis is usually obtained by means of fine needle aspiration biopsy or by plasma CT immunoassay. Some authors advocate the routine measurement of circulating CT in all patients with thyroid nodules (Pacini et al. 1994, Vierhapper et al. 1997), although the low incidence of MTC may warrant a careful evaluation of the cost/benefit ratio.

Prognosis and treatment effectiveness are largely related to the tumour stage (Saad et al. 1984, Brierley et al. 1996, Dottorini et al. 1996, Hundahl et al. 1998, Modigliani et al. 1998, Kebebew et al. 2000). The 10-year overall survival rate has been estimated at 75–76% for both US (Hundahl et al. 1998) and German (Raue 1998) patients. MEN 2A patients generally have a better prognosis than those with sporadic MTC (Bergholm et al. 1990); however, no differences in survival were seen when patients were matched for age and extent of disease (Samaan et al. 1988). This suggests that patients with sporadic carcinoma are commonly diagnosed later, when the disease is more advanced. As far as inherited MTC is concerned, FMTC seems to have the best survival rate, while MEN 2b has the worst (Grauer et al. 1990, Samaan et al. 1988, Nguyen et al. 1992). Early diagnosis is essential in patients with MTC, in order to obtain the best cure rate. Early surgery in gene carrier members, identified by means of molecular analysis, has now significantly improved the prognosis of inherited MTC (Wells et al. 1994).

Surgical treatment

The primary treatment of MTC is the surgical removal of all neoplastic tissue. Since local recurrence may ultimately prove fatal, aggressive and meticulous surgery is required. Accurate clinical staging and exclusion of concomitant pheochromocytoma are warranted before surgery. In the event of concomitant pheochromocytoma, adrenalectomy should be performed before thyroidectomy. Early surgery is recommended as soon as possible in adult carriers, and before the age of six in children with RET germline mutations (Telander et al. 1986, Kebebew et al. 2000). Considering that children with MEN 2b have a worse prognosis and an earlier clinical expression, surgery should not be delayed. On the other hand, gene carriers of a RET
The most common surgical approach is total thyroidectomy with central node dissection, bounded by the hyoid bone, sternal notch and internal jugular vein (Russel et al. 1983, Duh et al. 1989, Kallinowski et al. 1993). This surgical strategy is widely accepted in patients with non-palpable MTC identified by screening, but the need for more extensive neck dissection at first surgery remains a matter of debate in those who present a palpable mass. MTC gives early metastases to regional nodes; several reports state that cervical involvement occurs in 25–63% of cases, depending on the series considered (Hazard et al. 1959, Williams 1966, Chong et al. 1975, Rossi et al. 1980, Rougier et al. 1983). In patients with palpable unilateral MTC, Moley and DeBenedetti (1999) found lymph node metastases in 81% of central neck dissection specimens, in 81% of ipsilateral neck dissection specimens, and in 44% of contralateral neck dissection specimens. Thus, in patients with palpable tumours, routine total thyroidectomy with central and bilateral functional neck dissection has been recommended (Moley & DeBenedetti 1999). A systematic lymph-node dissection of the lower two-thirds of the jugulo-carotid chain has also been proposed as a routine procedure: should metastatic regional nodes be identified, a standard modified (functional) radical neck dissection is recommended (Schlumberger & Pacini 1999).

The parathyroid glands should be identified and preserved during surgery; if they appear to be normal, they can be left in place, or immediately transplanted in a sternocleidomastoid or in a non-dominant forearm muscle (Schlumberger & Pacini 1999). Permanent post-operative hyopoparathyroidism should be limited to approximately 1% (Van Heerden et al. 1987). Schlumberger & Pacini (1999) recommend the removal of three glands with reimplantation of a portion of the remaining gland in patients with concomitant hyperparathyroidism with diffuse parathyroid hyperplasia (MEN 2A syndrome).

Post-operative elevated CT levels are indicative of residual disease, commonly attributable to microscopic locoregional lymph-node involvement. A careful second operation, consisting of meticulous ultra-radical dissection, has been proposed in order to normalise calcitonin plasma levels and, presumably, to improve the cure rates. Tisell et al. (1986) reported normalisation of the circulating calcitonin levels in four out of eleven patients who had been submitted to a second operation following initial thyroidectomy. Buhr et al. (1993) achieved biochemical cure in all but one case among 14 patients treated with microsurgical dissection. Similar results were reported by Moley et al. (1993): in their series of patients, 9 out of 32 (28%) showed normal levels of stimulated calcitonin in the immediate postoperative period.

More recently, the same authors (Moley et al. 1997) obtained the normalisation of postoperative stimulated calcitonin levels in 17 out of 45 patients (38%) who had undergone a second operation. These more positive results probably occurred thanks to an accurate preoperative selection of the patients, which was carried out with a direct liver examination prior to the neck surgery; laparoscopic or open liver examination identified metastases in 10 patients (about 25% of the total), nine of whom had previously presented a normal computed tomography or magnetic resonance imaging (MRI) of the liver, who would otherwise have undergone a second neck operation with a curative intent (Tung et al. 1995, Moley et al. 1997).

A more conservative surgical management of patients with persistent post-operative hypercalcitoninaemia has been claimed by other authors, due to the indolent clinical course observed when residual disease is not macroscopically detectable (Van Heerden et al. 1990). In this series, the standard approach was observation alone, until clinical examination or imaging procedures identified patients undergoing aggressive course.

Long term follow-up data on a large series are needed to determine the most appropriate therapeutic approach in patients with occult disease.

Palliative surgery for metastatic MTC is sometimes a necessary approach in current clinical practice. Neurological involvement by vertebral metastases can require decompressive surgery. Resection of brain metastases could be of symptomatic value (Chiu et al. 1997), although an increased survival rate has not been proven.

Finally, non-surgical palliative procedures in advanced MTC may include both percutaneous ethanol injection in the thyroid bulk and treatment of liver metastases with transcatheter arterial embolisation followed by ethanol percutaneous injection, as successfully reported in a recent anecdotal case (Isozaki et al. 1999).

Detection of residual or recurrent disease

Patients with post-operative normalisation of circulating calcitonin and/or CEA levels are commonly considered surgically cured (Marsh et al. 1995). Due to the long half-life of circulating CEA and the different half-lives of the calcitonins (Fugazzola et al. 1994), serum marker measurements should be performed 2 months following surgery (Schlumberger & Pacini 1999). In patients with normalisation of the tumour markers, stimulated peak plasma calcitonin levels have been reported to be more effective than basal concentrations in detecting occult disease after thyroidectomy (Tisell et al. 1996, Giuffrida & Gharib 1998).

In patients with residual disease, further evaluations should be performed in order to plan the appropriate treatment. The initial diagnostic modality should be high resolution ultrasonography, with ultrasound-guided fine
needle aspiration biopsy for the cytological confirmation of the equivocal cases (Sutton et al. 1988). Non invasive imaging procedures include computed tomography and/or MRI, even though their sensitivity in identifying occult disease has not been satisfactorily demonstrated (Shulkin & Shapiro 1990, Abdelmoumene et al. 1994).

Some authors (Tung et al. 1995, Moley et al. 1997) reported that diagnostic laparoscopy of the liver was more sensitive than computed tomography and MRI, because the direct examination and biopsy of the liver showed small deposits of metastatic MTC in several patients with normal imaging procedures.

Radioisotopic procedures have been widely used to detect metastatic MTC. Scanning with 131-I-metaiodobenzylguanidine (131-I-MIBG) (Clarke et al. 1988, Hoefnagel et al. 1991) and with 111-In-octreotide (Berna et al. 1995, Baudin et al. 1996) have shown limited sensitivity, with detection of the disease in less than 30–50% of the cases considered. Technetium-99m-dimercaptosuccinic acid, 99m-Tc(V)DMSA, revealed high sensitivity in the identification of both bone and soft tissue metastases (Clarke et al. 1988, Patel et al. 1988, Ugur et al. 1996); nevertheless, these results have not been confirmed by other authors (Verga et al. 1989, Berna et al. 1995). Only a slight advantage over planar scanning was observed whilst performing radionuclide imaging with the single photon emission computerised tomography technique (SPECT) (Udelsman et al. 1993, Berna et al. 1995). Immuno-scintiscan procedures with radiolabelled monoclonal antibodies (MoAbs), such as anti-calcitonin MoAbs and anti-CEA MoAbs, have been proposed (Goldenberg et al. 1983, Manil et al. 1989). Behr et al. (1997) studied fourteen patients with anti-CEA MoAbs scintigraphy, and reported a higher sensitivity of this method than that of conventional diagnostic modalities, especially for more aggressive forms of MTC. High costs and difficult availability of radiolabelled MoAbs limit the routine use of this diagnostic procedure. Preliminary results on fluorine-18-glucose (FDG) positron emission tomography (PET) are encouraging (Gasparoni et al. 1997, Musholt et al. 1997). The latter authors studied 10 patients with persistent or recurrent MTC after thyroidectomy, and showed that FDG-PET imaging is more sensitive but less specific in detecting the regional metastatic lesions in comparison with computed tomography or MRI respectively. As a whole, radionuclide scanning procedures have the capability to detect sizeable tumours, but demonstrate poor accuracy when searching for occult disease.

More invasive technology has sometimes been applied to identify micrometastases. Selective venous sampling catheterisation with calcitonin measurements has been demonstrated to be a valuable method for the localisation of occult disease, in order to obtain microsurgical removal of the neoplastic tissue (Wells et al. 1982, Frank-Raue et al. 1992, Abdelmoumene et al. 1994, Tisell et al. 1996). Pentagastrin-stimulated sampling may enhance the diagnostic power of the procedure.

**External radiotherapy**

Responses to external beam radiotherapy in patients with MTC are commonly considered unsatisfactory (Williams et al. 1966, Reinhardt et al. 1995). Samaan et al. (1988) retrospectively studied 57 patients receiving 2500–6000 rads over 5 weeks. No improvement in overall survival rates was observed when patients treated with surgery alone or with a combination of surgery and radiation therapy were matched for age and for the involvement of cervical nodes, soft tissue and distant metastases.

Other researchers reported external radiotherapy to be useful in selected groups of patients. Steinfield (1977) reported local control in three patients with widespread metastases who were initially diagnosed with neck masses and lymphadenopathy. Tubiana et al. (1985) evaluated retrospectively 80 patients treated with surgery alone and 35 receiving external radiotherapy in addition to surgery. Even though the relapse-free survival and total survival rates were similar in the two groups, the results of radiotherapy were considered favourable because the irradiated patients initially had a higher degree of disease involvement and poorer prognostic factors (lower radicality of surgery excision and more extensive extrathyroid and nodal diffusion). In this series, eight patients underwent radiotherapy for inoperable tumours: of these, one presented complete remission, two a regression of more than 50% of the tumour and four experienced significant palliation, with a reduction of less than 50% of the bulk. More recent experiences confirm the positive results of external radiotherapy, which can induce long-term stabilisation in some patients with inoperable or incompletely excised tumours (Schlumberger & Pacini 1999). Brierley et al. (1996) studied 40 patients with high risk of recurrence (microscopic residual disease, extraglandular invasion or lymph-node involvement): the local/regional relapse-free rate at 10 years was significantly higher in 25 patients with post-operative beam radiation as compared with 15 patients treated with surgery alone (86% vs 52%).

In conclusion, external radiotherapy should be considered to improve local/regional tumour control in patients with postoperative gross residual disease or inoperable tumours.

**Radionuclide therapy**

131-Iodine treatment has not been demonstrated to be of significant value in the treatment of MTC (Hellman et al. 1979, Saad et al. 1983) and has now been abandoned. Since 131-I-MIBG is taken-up by a number of MTC patients, its administration has been proposed as a radiometabolic
treatment for those patients who present a significant scintigraphic uptake. Published reports on small series suggest an overall response rate of approximately 40%, although symptom palliation may be achieved in a higher percentage of patients (Clarke et al. 1987, Clarke 1991, Hoefnagel et al. 1991, Schwartz & Delisle 1991). Only a minority of MTC patients shows a significant uptake; in addition, high costs and unpredictable response to therapy limit the role of 131-I-MIBG as a treatment for the disease.

Radiometabolic treatment with anti-CEA labelled monoclonal antibodies (anti-CEA MoAbs) has also been proposed. A recent trial enrolled 15 patients with advanced disease to receive 131I anti-CEA MoAbs, administered at the maximum tolerated dose to the bone marrow tissue: seven patients had a median of 55% reduction in tumour markers, one patient showed dramatic improvement in the mass size and eleven patients experienced stabilisation of the disease lasting 3+ to 26+ months (Juweid et al. 1999). Further studies are needed to confirm these preliminary results.

**Treatment with biological response modifiers**

Therapeutic administration of biological response modifiers, such as hormones and cytokines, has been a matter of investigation in several types of neuroendocrine tumours including MTC.

Both somatostatin-like immunoreactivity (Roos et al. 1981, Lamberts et al. 1991) and high-affinity somatostatin receptors (Lamberts et al. 1991, Reubi et al. 1991) have been identified in MTC. The experimental observation that somatostatin can decrease calcitonin secretion, both in vitro and in vivo (Gordin et al. 1978, Bertagna et al. 1980, Pacini et al. 1989), suggested a potential role for endocrine treatment in patients with MTC. As in other endocrine tumours (Kraenzlin et al. 1985, Anderson & Bloom 1986, Kvol 1988), octreotide, a long-acting somatostatin analogue, demonstrated some promising but inconsistent positive results in a few cases of advanced MTC. Both refracted doses and continuous subcutaneous administration of the drug have been tested. Variable doses have been used in different studies, ranging from 0.05 to 4 mg administered daily.

As a significant decrease in tumour mass has never been recorded, the available clinical studies have focused on the reduction of calcitonin levels and the improvement of hormone-related symptoms such as diarrhoea and flushing.

Low dose octreotide, administered acutely or short term, generally failed to inhibit CT secretion. Schrezenmeir et al. (1986) did not obtain any reduction of CT plasma levels in three patients treated with 0.05 mg twice daily; using the same dose, Jenkins et al. (1987) found no effect on circulating CT in a patient with advanced MTC associated with pancreatic neoplasia, although diarrhoea promptly disappeared; other authors (Ahlman & Tisell 1987) reported no change in CT levels with 0.1 mg octreotide per day; finally, no significant effect of an acute four-hour infusion of octreotide was found in eleven patients tested by Modigliani et al. (1988).

As far as long term treatment is concerned, studies performed on patients with metastatic MTC gave conflicting results. Fourteen patients were treated for 90 days with continuous subcutaneous (0.5 mg daily) octreotide administration, and no significant decrease of calcitonin levels nor any symptomatic/morphological improvement were observed (Modigliani et al. 1992). In another series, seven patients with progressive MTC, given 0.2–2 mg octreotide 2–3 times per day for 3–9 months, showed low response on tumour markers, control of diarrhoea and tumour growth (Frank-Raue et al. 1993). High dose octreotide (4 mg/day subcutaneously) administered continuously for up to 12 months, was also ineffective in one patient with advanced disease reported by Zlock et al. (1994).

More favourable results were obtained in other studies. Three times daily subcutaneous injections of rising doses of octreotide (0.3 to 1.5 mg per day) decreased CT levels by 25–35% in 5/18 patients studied by Guliana et al. (1989); the inhibitory effect was more consistent in patients with less extensive disease. Clements et al. (1986) reported an inhibitory effect of 0.5 mg octreotide on CT levels of up to 40% in two out of three patients. Mahler et al. (1990) observed symptomatic relief in all three patients treated with continuous subcutaneous octreotide infusion of 0.6–1 mg/day via an automatic pump, although the decrease of CT and CEA levels was partial and transient; these beneficial effects were lost after 3–17 months, despite increasing the dose to 1.5–2 mg/day. Symptomatic improvement has also been shown by others (Jerkins et al. 1987, Smid & Dullaart 1992), although significant reduction of tumour bulk was never reported.

Human recombinant α-interferon (rIFN-α) has been shown to exert some therapeutic effect on advanced neuroendocrine tumours (Oberg et al. 1983, Moertel et al. 1989, Grohn et al. 1990, Biesma et al. 1992, Bajetta et al. 1993). The Italian Trials in Medical Oncology Group (Bajetta et al. 1993) reported subjective symptomatic relief in 64% of patients. This series included one patient affected by MTC with a mediastinal node of 3 cm diameter, who experienced a complete remission as assessed by computed tomography scan.

Since a combination of rIFN-α and octreotide obtained a dramatic response in a case of metastatic carcinoid (Joensuu et al. 1992), the same therapeutic schedule has been tested by Lupoli et al. (1996) in advanced MTC. They treated eight patients with one-year subcutaneous octreotide administration (0.30 to 1.15 mg/day) in combination with intramuscular rIFN-α-2b 5 00 000 IU three times a week. Five patients experienced symptomatic improvement; a decrease in plasma CT was observed in six cases, with no
reduction in the size of metastases. The same authors recently evaluated the effects of the slow release somatostatin analogue lanreotide in combination with interferon α-2b. Despite no objective complete or partial responses being recorded, symptomatic benefit was achieved in six out of seven patients (Vitale et al. 2000).

In conclusion, several clinical studies have excluded significant antiproliferative activity of octreotide and/or other biological response modifiers; nevertheless, they may suggest a symptomatic role in a minority of patients with advanced MTC.

Recent experimental studies, performed on animal models of MTC, have opened a fascinating perspective for gene therapy. It has been demonstrated that the transduction of the interleukin-2 (IL-2) gene and the herpes simplex 1 timidine kinase (HSV1–TK) gene is able to facilitate cellular apoptosis in the MTC cells injected and to enhance the endogenous mechanisms of immunosurveillance in the host animals (Zhang et al. 1998, Soler et al. 1999); moreover, gene therapies showed the capability to sensitisise MTC cells to the action of immunoactive/cytotoxic drugs, such as IL-2 and gancyclovir (Soler et al. 1999, Zhang & DeGroot 2000). These observations may have importance in view of future applications of immunoregulatory gene therapies for human MTC.

Chemotherapy

MTC usually shows an indolent course even at the stage of distant spread and is associated with long term survival rates (Brierley et al. 1996, Dottorini et al. 1996, Modigliani et al. 1998, Schlumberger & Pacini 1999). Thus, chemotherapy is not necessary in the management of most cases of progressive disease. Usually, symptomatic or palliative treatment by means of external radiotherapy, selective surgery of metastases, and supportive drugs for pain or diarrhoea, is adequate. Chemotherapy could be recommended in a minority of patients presenting rapidly progressive metastatic tumour, which represents an unpredictable event in the natural history of the disease.

The low frequency of metastatic MTC has precluded studies either involving a large patient population or randomised clinical trials. As a result, the response rate to different chemotherapeutic regimens is not well known.

Several clinical observations have been reported, mainly on a limited number of patients, who were at times included in heterogeneous series with other types of thyroid cancer and/or neuroendocrine tumours. The available clinical reports are listed in Table 3.

The response criteria to the treatment used in the different studies are not homogeneous. A reduction of calcitonin levels is often reported (Burgess & Hill 1978, Husain et al. 1978, Weiss 1978, Stepanas et al. 1979, Leight et al. 1980, Kessinger et al. 1983, Sridhar et al. 1985, Petursson 1988), but it does not appear to be adequate in evaluating the partial responses, because of its inconstant correlation with the mass reduction. In most reports, the objective response was determined by the reduction in measurable tumour mass, which appears to be acceptable for clinical purposes.

The most frequently used drug is doxorubicin, alone or combined with other cytotoxic agents. The response rates are lower than the previously reported ones (Burgess & Hill 1978), not exceeding 20–30% of patients; the response has usually been partial and short-lasting (a few months) (Husain et al. 1978, Leight et al. 1980, Harada et al. 1981, Simpson et al. 1982, Rougier et al. 1983, Droz et al. 1984, Shimaoka et al. 1985, Hoskin & Harmer 1987). The combination of doxorubicin with cis-platinum has not achieved a significantly higher response rate, but major toxic effects have been observed (Table 4) (Shimaoka et al. 1985, Sridhar et al. 1985, Williams et al. 1986). De Besi et al. (1991) reported encouraging results in a small series of eight patients with advanced MTC, included in a larger population of thyroid tumours of various histology, which were treated with a doxorubicin, cis-platinum and bleomycin multidrug combination: they observed four partial responses and a stabilisation of disease lasting for less than 4 months in the remaining patients.

Experience in the treatment of metastatic MTC with other cytotoxic drugs is even more limited. In small series or in anecdotal cases, several chemotherapeutic regimens have been tested, including cis-platinum (Kamalakar et al. 1977, Droz et al. 1984, Williams et al. 1986, Hoskin & Harmer 1987), etoposide (Fiore et al. 1984, Hoskin & Harmer 1987), vindesine (Rossoff et al. 1979, Scherubl et al. 1990), rubidazone (Stepanas et al. 1979), dacarbazine (DTIC) (Kessinger et al. 1983, Petursson 1988, Orlandi et al. 1994, Wu et al. 1994, Schlumberger et al. 1995, Bajetta et al. 1998), 5-fluorouracil (5-FU) (Petursson 1988, Orlandi et al. 1994, Bajetta et al. 1998), cyclophosphamide (Weiss 1978, Wu et al. 1994), vincristine (Wu et al. 1994), and streptozocin (Weiss 1978, Schlumberger et al. 1995) given either as single agents or in combination, with conflicting results (Table 4).

Some of these drugs were tested in MTC because of their demonstrated activity in other neuroendocrine tumours, such as carcinoids or islet cell carcinomas; good response rates have been reported with regimens containing 5-FU, DTIC and streptozocin (Moertel et al. 1980, Kessinger et al. 1983, Moertel 1983, Engstrom et al. 1984, Bajetta et al. 1998).

As far as MTC treatment is concerned, Petursson (1988) first described a complete clinical and biochemical response to combination chemotherapy with DTIC (250 mg/m²) and 5-FU (450 mg/m²) administered daily for 5 days per month, in a patient with advanced MTC metastatic to the lung and skin.

Subsequently, we treated seven patients, 6 females and 1 male, bearing progressive locally advanced or metastatic
Table 3 Antiproliferative agents in medullary thyroid carcinoma.

<table>
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<tr>
<th>Drugs</th>
<th>References</th>
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<tr>
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<td>—</td>
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<tr>
<td>DOXO + CDDP</td>
<td>Shimaoka et al. (1985)</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>DOXO + CDDP</td>
<td>Williams et al. (1986)</td>
<td>6</td>
<td>—</td>
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<tr>
<td>DOXO + CDDP</td>
<td>Droz et al. (1984)</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>DOXO + CDDP</td>
<td>Sridhar et al. (1985)</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>DOXO + VCR + BLM</td>
<td>Hoskin &amp; Harmer (1987)</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>DOXO + CDDP + BLM</td>
<td>De Besi et al. (1991)</td>
<td>8</td>
<td>1</td>
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<td>CDDP</td>
<td>Hoskin &amp; Harmer (1987)</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>CDDP</td>
<td>Leight et al. (1980)</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>CBDCA</td>
<td>Hoskin &amp; Harmer (1987)</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>VP16</td>
<td>Fiore et al. (1984)</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>MTX</td>
<td>Hoskin &amp; Harmer (1987)</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>DOXO + CDDP + VDS</td>
<td>Scherubl et al. (1990)</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>VDS</td>
<td>Rossoff et al. (1979)</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>DTIC + 5FU</td>
<td>Kessinger et al. (1983)</td>
<td>1</td>
<td>—</td>
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<tr>
<td>DTIC + 5FU</td>
<td>Petrusson (1988)</td>
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<td>DTIC + 5FU</td>
<td>Personal data</td>
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<td>—</td>
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<tr>
<td>DTIC + 5FU + EPX</td>
<td>Bajetta et al. (1998)</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>DTIC + CTX + VCR</td>
<td>Wu et al. (1994)</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>5FU-DTIC or 5FU-STZ</td>
<td>Schlumberger et al. (1995)</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>DOXO + CTX + STZ</td>
<td>Weiss (1978)</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Rubidazone</td>
<td>Stepanas et al. (1979)</td>
<td>1</td>
<td>—</td>
</tr>
</tbody>
</table>

Total: 144 patients (3 (2%) complete response, 39 (27%) partial response)

DOXO, Duxorubicin; CDDP, Cisplatinum; VCR, Vincristine; BLM, Bleomycin; CBDCA, Carboplatin; VP16, Etoposide; MTX, Methotrexate; VDS, Vindesine; DTIC, Decarbazine; 5FU, 5-Fluorouracil; EPX, Epirubicin; STZ, Streptozocin.

MTC, with 5-day intravenous courses of DTIC (250 mg/m²) and 12-h daily intravenous infusions of 5-FU (450 mg/m²), given every 4 weeks. Partial results of this study have already been published (Orlandi et al. 1994). Four partial responses, lasting 9, 20, 54 and 40+ months respectively, were observed; another patient had stable disease lasting 35 months; ultimately, two patients showed progressive disease (Table 5). At present, two patients are alive and present local disease. The treatment was well tolerated, even in older patients, contrasting with the severe myelotoxicity observed elsewhere (Petursson 1988); the long-lasting (12-h) infusion of 5-FU may be an explanation for the lower toxicity. In conclusion, four responses over seven patients appear to be of clinical interest, although all remissions were partial and short-lasting (Table 5). Among the responding patients, in only one case did calcitonin levels drop after chemotherapy; in the three remaining patients, the reduction in tumour size was not associated with calcitonin lowering.

Other authors (Schlumberger et al. 1995), by alternating 5-fluorouracil-DTIC and 5-fluorouracil-streptozocin combinations in 20 patients with metastatic disease, achieved 3 partial tumour responses and 11 cases of stabilisation of the disease, with an improvement of the performance status in 7 patients; no significant toxicity occurred. A partial response was recently reported in the only case of advanced MTC enrolled within an heterogeneous neuroendocrine tumour series of 25 patients, using the combination of 5-FU, DTIC and doxorubicin (Bajetta et al. 1998). Another clinical trial combined DTIC, cyclophosphamide and vincristine (Wu et al. 1994) in 7 patients: 2 partial responses, 2 stable disease and 3 progressive disease were reported.

Comparing the results of the different chemotherapeutic treatments is very difficult because of the nonhomogeneous selection of the patients, the different chemotherapeutic protocols and the response evaluating criteria. When the experiences from different reports are compared, doxorubicin and combination doxorubicin + cisplatinum or 5 FU + DTIC have similar response rates (Table 4). Due to the very low

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Table 4 Overall response to single or combination antiproliferative agents in metastatic MTC.

<table>
<thead>
<tr>
<th>Drugs and references</th>
<th>No. of patients</th>
<th>Complete response</th>
<th>Partial response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duxorubicin</td>
<td>41</td>
<td>1 (2%)</td>
<td>12 (29%)</td>
</tr>
<tr>
<td>Burgess &amp; Hill (1978)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shimaoka et al. (1985)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Husain et al. (1978)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Leight et al. (1980)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harada et al. (1981)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Droz et al. (1984)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simpson et al. (1982)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duxorubicin and cis-platinum-containing regimens</td>
<td>47</td>
<td>1 (2%)</td>
<td>12 (25%)</td>
</tr>
<tr>
<td>Shimaoka et al. (1985)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams et al. (1986)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Droz et al. (1984)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sridhar et al. (1985)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Besi et al. (1991)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scherubl et al. (1990)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decarbazine and/or 5-fluorouracil-containing regimens</td>
<td>37</td>
<td>1 (3%)</td>
<td>9 (24%)</td>
</tr>
<tr>
<td>Personal data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petursson (1988)</td>
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<td></td>
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</tr>
<tr>
<td>Bajetta et al. (1998)</td>
<td></td>
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<td>Schlumberger et al. (1995)</td>
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<td></td>
</tr>
<tr>
<td>Wu et al. (1994)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kessinger et al. (1983)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table 5 Clinical features of the patients treated with 5-fluorouracil and decarbazine and response to chemotherapy.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Sites of disease before treatment</th>
<th>Stage</th>
<th>Response</th>
<th>Time to progression (months)</th>
<th>Survival (months)</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>67</td>
<td>Locally advanced disease</td>
<td>III</td>
<td>SD</td>
<td>35</td>
<td>35</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>26</td>
<td>Lung, liver</td>
<td>IV</td>
<td>PD</td>
<td>—</td>
<td>57</td>
<td>MTC</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>69</td>
<td>Lung, liver, bone, retina</td>
<td>IV</td>
<td>PR</td>
<td>9</td>
<td>11</td>
<td>MTC</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>71</td>
<td>Liver</td>
<td>IV</td>
<td>PR</td>
<td>20</td>
<td>32</td>
<td>MTC</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>22</td>
<td>Locally advanced disease</td>
<td>III</td>
<td>PR</td>
<td>54+</td>
<td>78 (AWD)</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>36</td>
<td>Locally advanced disease</td>
<td>III</td>
<td>PR</td>
<td>40+</td>
<td>40 (AWD)</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>57</td>
<td>Lung, lymph-nodes</td>
<td>IV</td>
<td>PD</td>
<td>—</td>
<td>33</td>
<td>MTC</td>
</tr>
</tbody>
</table>

MTC, medullary thyroid carcinoma; PR, partial response; SD, stable disease; PD, progressive disease; AWD, alive with disease.

toxicity, according to our personal experience, we think that
the medical treatment with regimens containing 5-FU and
d tic could be indicated as first line treatment of advanced
raptly progressive MTC. Further controlled studies on large
series are warranted.

In conclusion, chemotherapy with different protocols of
cytostatic drugs has shown a certain degree of activity in
terms of tumour response, but no benefit has been
demonstrated for survival. The lack of activity in a consistent
percentage of patients may be indirectly explained by
experimental observations on cultured human MTC cells in
which the overexpression of the multidrug resistance mdr-1
gene has been reported (Larsson & Nygren 1990, Yang et al.
1991). In vitro studies have demonstrated that the
overexpression of the mdr-1 gene and its resistance to
duxorubicin can be partially reversed by cyclosporin,
verapamil and other investigational drugs (Massart et al.
1995, 1998). Such results may stimulate further basic and
clinical advancement of research, in order to improve the
medical approach to advanced MTC.

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