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Therapeutic potential of octreotide in the treatment of liver metastases

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Octreotide is a synthetic analogue of somatostatin that has clear inhibitory effects on the growth of many animal and human cell lines, including colorectal cell lines both *in vitro* and *in vivo*. Colorectal cancer metastatic to the liver is clinically important, both in terms of the number of patients affected and the lack of any effective treatment for the majority of patients. Octreotide inhibits the growth of colorectal liver tumour in a number of experimental models and, in at least three tumour types, inhibits the growth of established micro-metastases. The precise mechanism of action is not known. However, the drug is likely to be most beneficial in the treatment of liver metastases when the tumour burden is relatively small. The available evidence, although experimental, suggests that octreotide may also have a beneficial effect on the development of liver metastases when used as an adjuvant to surgery in colorectal cancer and this area warrants urgent clinical investigation. The cytotoxics which are currently used as an adjuvant to surgery for colorectal cancer have unpleasant side effects which can be life-threatening. There will also be a proportion of patients who have undergone a truly curative resection of their tumour and will thus be treated unnecessarily. The potential benefits of octreotide in the adjuvant setting, although promising, remain speculative, but octreotide has an acceptably low incidence of side effects and can be administered safely for a prolonged period of time.

Key words: Liver metastases, octreotide, adjuvant, surgery, colorectal cancer.

Introduction

The prognosis for patients with metastatic liver disease remains poor, with most patients dying within 1 year of diagnosis. The most common hepatic metastases are adenocarcinomas arising from primary gastrointestinal tumours, and of these colorectal cancers are the most frequent. Metastases derived from colorectal cancer are of particular interest as the liver is often the only site of recurrent disease. Hepatic metastases also frequently occur in patients with pancreatic and gastric carcinomas, both depressingly common malignancies. The treatment of patients with liver metastases is generally unsatisfactory and remains a significant clinical challenge. Therapy for unresectable liver metastases relies mainly on either single agent or combination chemotherapy which is largely ineffective at present. At best, chemotherapeutic regimens (either systemic or targeted to the liver) result in only a modest increase in survival and often at the expense of serious side effects. Adjuvant therapy following a potentially curative resection of a colorectal primary tumour aims to prevent occult or micro-metastases developing into overt tumours. There has recently been some success in the adjuvant treatment of colorectal cancer,[1] but all these regimens have involved administration of potentially toxic chemotherapy to a large number of patients with benefit being seen in only a minority. Furthermore, a proportion of patients will have undergone a curative resection for a colorectal primary tumour and will therefore be treated unnecessarily with potentially toxic chemotherapeutic agents. Consequently, there is a need for a safe and effective treatment for both established liver metastases arising from gastrointestinal cancers and micro-metastases present in the liver following surgical resection of colorectal cancers.

Recently, numerous reports have indicated that the growth of some gastrointestinal tumours is dependent on a number of hormones and growth factors such as gastrin, secretin bombesin, insulin-like growth factor-1 and epidermal growth factor.[2,3] The possibility of inhibiting the release or blocking the end-organ effect of these factors on tumour growth has therefore been explored in recent years using somatostatin and its analogues.

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Somatostatin is a cyclic 14-amino-acid peptide and is widely distributed throughout the central nervous system and gastrointestinal tract. It inhibits the release and end-organ action of many endocrine secretions and also has a direct anti-proliferative action on many tumour cells.[3–5] Any potential therapeutic benefits of somatostatin in the treatment of gastrointestinal malignancy are, however, severely limited by its short plasma half-life.

Octreotide is a synthetic analogue of somatostatin in which the four amino acids responsible for the biological activity of the native hormone are retained. However, incorporation of amino-terminal D-phenylalanine, caboxyl-terminal amino-alcohol, D-tryptophan and a cysteine bridge makes octreotide more resistant to enzymatic degradation than somatostatin, and consequently it has a longer plasma half-life than the native hormones and can be administered subcutaneously. Octreotide has been widely used to treat a number of endocrine and gastrointestinal disorders,[6] and of all the somatostatin analogues it is the only one that has been extensively used clinically and whose side-effect profile and long-term effects are well documented. In clinical practice octreotide is very useful for the treatment of functioning pituitary and neuroendocrine tumours of the gastrointestinal tract, but its role in the treatment of other tumours is less well defined.[3–5]

Several mechanisms of action have been postulated for the inhibitory effect of octreotide on the growth and development of tumour cells. These include a direct receptor-mediated anti-proliferative effect, a reduction in the circulating levels of growth factors such as growth hormone, prolactin and insulin-like growth factor and inhibition of the secretion of autocrine growth factors which may be important in tumour cell growth.

During the past 5 years we have studied the effects of octreotide in the treatment of liver metastases, and have demonstrated that it may be a useful agent in this area. In addition to any anti-proliferative effects of octreotide on tumour cells, the analogue also causes changes in liver blood flow and stimulates hepatic reticulo-endothelial system activity, both of which may inhibit the growth and development of liver tumours.

Experimental studies in the treatment of liver metastases with octreotide

Octreotide is effective in reducing tumour growth in a number of experimental models of liver metastases. Nott *et al.*[7] were the first to demonstrate that octreotide significantly reduced the growth of liver tumour in rats. In this study tumours were induced in rats by the intraportal injection of Walker cells followed by treatment with octreotide (2 μg twice a day) for 3 weeks. There was a significant reduction in tumour growth in the treated rats compared to the control animals (hepatic replacement 7 versus 30%). Octreotide had no effect on the growth of Walker cells injected into the flanks of rats, and *in vitro* the analogue actually stimulated the growth of Walker cells. The authors concluded that the effect of octreotide in inhibiting tumour growth was unique to tumours located in the liver. Walker cells are highly malignant, poorly defined carcinosarcomas and will grow rapidly in a number of species. In the liver they produce confluent hypervascular tumours which are morphologically dissimilar from most metastases occurring in man. Therefore, Walker cells are perhaps not the most suitable cell line to use in evaluating potential therapies for hepatic metastases.

More recently, we have further investigated the effects of octreotide on the growth and development of hepatic tumours derived by intraportal injection of three other tumourigenic cell lines.[8] The HSN cell line is a fibrosarcoma which produces discreet hypovascular tumours in syngeneic rats after their intraportal injection. The WB2054M and K12Tr cell lines are both colonic adenocarcinomas derived from carcinogen-induced tumours in syngeneic rats. Both these cell lines produce discreet hepatic tumours following their intraportal injection which are histologically very similar to human colorectal liver metastases. Octreotide significantly inhibited the growth of all three cell lines in the liver when treatment was delayed for either 18 h or 1 week following their intraportal injection. Since micro-metastases are present in the liver 1 week after intraportal inoculation of the three tumourigenic cell lines, the results of this study indicate that octreotide inhibits the growth of established micro-metastases. Furthermore, since no established hepatic tumour was eliminated by octreotide therapy, the results of this study suggest that the effect of the analogue on the growth of liver metastases may be one of retardation rather than a cytocidal effect. HSN, WB2054M and K12Tr tumorigenic cells all have low-affinity somatostatin receptors on their surfaces and cell proliferation is inhibited by octreotide *in vitro*.[8]

In a similar study, Van Eijck *et al.*[9] also demonstrated that octreotide inhibited the growth and development of liver tumours in the rat. In this

study, hepatic tumours were induced by intraportal inoculation of the syngeneic pancreatic tumour cell line CA 20948. Octreotide (15 μg intraperitoneally twice a day for 28 days) significantly reduced both the number of tumours and the liver weight in treated rats compared to control animals. CA 20948 cells have high-affinity somatostatin receptors on their surfaces. In contrast, octreotide had no effect on the growth of a receptor-negative colonic tumour cell (CC 531) after intraportal inoculation. The results of this study thus suggest that the ability of octreotide to inhibit the growth and development of hepatic tumours is dependent on the presence of somatostatin receptors on the surface of the tumourigenic cells.

The effects of somatostatin analogues on the growth of human colonic tumour cells in the livers of nude mice have been investigated in two studies. Qin *et al.*[10] investigated the effect of RC 160 on the growth of hepatic tumours induced by the intrasplenic injection of two established human colon cancer cell lines derived from primary colon adenocarcinomas (320 DM and WidR). Treatment with RC 160 not only significantly reduced the incidence of liver tumours but also increased survival in octreotide-treated mice. Compared to the control mice, bromodeoxyuridine labelling also demonstrated a decrease in cellular proliferation in the tumours of the octreotide-treated mice. Furthermore, the cytostatic effect of RC 160 was evident from the reduction in DNA and protein contents of the tumour tissue of octreotide-treated mice. Similarly, Stewart *et al.*[11] investigated the effect of octreotide on the growth and development of C 170 human colonic tumour cells following their intrasplenic injection into nude mice. Octreotide (given by a mini-osmotic pump at a dose of 50 μg/kg for 28 days) significantly reduced the weight and percentage hepatic replacement of liver by tumour compared to control mice. Carcino-embryonic antigen levels in octreotide-treated mice were also significantly lower than in control mice.

The dose of octreotide used in the above experiments was very variable. A relatively low dose of about 6 μg/kg twice a day was used in two studies.[7,8] This dose was based on previous experimental work investigating the effects of octreotide on hepatic haemodynamics and reticulo-endothelial system activity, and could be reasonably scaled up to treat patients. A higher dose of 50 μg/kg per day was used by Stewart *et al.*[11] and this was given continuously over a 24-h period using an osmotic pump. Van Eijck *et al.*[9] similarly elected to use a relatively high dose of 50 μg octreotide intraperitoneally twice a day on the basis of a previous study on the effects of the somatostatin analogue on the growth of pituitary tumour cells in rats. In the study with analogue RC 160, a very high dose of 2000 μg/kg was used, again based on previous work.[10] It remains to be established whether or not a lower dose of octreotide may have had a similar effect on the growth of the hepatic tumours, but nevertheless, even in large doses, the analogue was well tolerated with no apparent side effects.

The above reports clearly show that octreotide significantly inhibits the growth of liver tumours in various models of hepatic metastases. Six of the cell lines investigated were derived from colonic tumours (three human) and it is perhaps not surprising that most effort appears to be directed towards the possible treatment of colorectal cancer-derived liver metastases as these form by far the most important clinical group. Liver tumours induced by five out of six of these colonic adenocarcinomas were significantly inhibited by octreotide treatment.

Mechanisms of action of octreotide in inhibiting the growth of liver tumours

Effects on growth factors and hormones

Any mechanism whereby octreotide inhibits tumour growth outside the liver would also be expected to be relevant to the inhibition of tumour growth within the liver. Octreotide is well known to suppress the release and end-organ action of growth factors and hormones that may be trophic with respect to the growth of liver metastases. For example, the release and action of growth hormone, insulin, gastrin, insulin-like growth factor-1, epidermal growth factor and transforming growth factor-α are all affected by octreotide and may be important in the mechanism by which the analogue reduces tumour growth in the liver. These mechanisms are discussed in detail elsewhere.[3–5]

Receptor-mediated effects

A direct receptor-mediated effect on tumour cell proliferation may also be important in the inhibition of liver tumour growth by octreotide. Octreotide had no effect on the growth of the somatostatin receptor-negative cell line CC 531.[9] In contrast, somatostatin receptors have been identified on pancreatic carcinoma cell line CA 20948,[9] rat colon

cancer cell lines WB2054M and K12Tr and on HSN cells,[12] and the growth of all these tumourigenic cells in the liver is inhibited by octreotide. The receptor status of the other cell lines used to induce liver tumours is not known but could clearly be important.

At least five somatostatin[13–15] receptor subtypes have been cloned and partially characterized (Table 1). All five somatostatin receptor subtypes belong to the seven-transmembrane-spanning receptor family with a potential for G-protein linkage and for inhibiting adenyl cyclase with a resultant reduction in intracellular cyclic AMP. Even though each receptor subtype can bind both somatostatin 14 and somatostatin 28 with approximately equal affinity, there are marked differences in the binding of the shorter analogues of the native hormone. For example, octreotide has a high binding affinity for SSTR2 but little or no affinity for SSTR1 and SSTR4. Octreotide also has a high affinity for SSTR5 but only an intermediate affinity with SSTR3 (Table 1). In addition, intestinal mucosa and malignant gastrointestinal tissue (stomach and colon) have been shown to have low-affinity high-capacity somatostatin receptors.[16,17] The functional significance of this distinct receptor subtype requires further study.

Table 1. Somatostatin receptor subtypes and the binding of octreotide

Receptor subtype	Octreotide binding	Selection for somatostatin 14 and somatostatin 28
SSTR1 Yamada	–	28 = 14
SSTR2 Yamada	++	28 = 14
SSTR3 Yamada	+	28 = 14
SSTR4 Bruno	–	28 = 14
SSTR5 O'Carrol	++	28 > 14

++, High binding affinity; +, intermediate binding affinity; –, no affinity.

Any direct anti-proliferative effect of octreotide on tumourigenic cells may depend on the type of somatostatin receptor present. Providing the anti-proliferative effect of octreotide subserves the receptor-binding affinity of the analogue then the inhibitory effects of the analogue on the growth and development of tumour will depend on the receptor subtype present on the cell. Radiolabelled somatostatin ligand was not displaced in gastric and colonic tumours by octreotide although analogues RC 160 and somatatuline did displace native somatostatin and both showed high affinities for the receptors. Consequently, octreotide might be expected to have little or no effect on these particular tumour types. In contrast, the drug may have a marked effect on the growth of tumours with high-affinity receptors. Differences in receptor-binding affinity for octreotide do not, however, explain the efficacy of the analogue octreotide in inhibiting the growth of a large number of human colon cancer cells both *in vitro* and *in vivo*, suggesting that receptor-independent effects on cell proliferation are also important. Clearly, further studies are necessary to elucidate the mechanism whereby octreotide exerts an anti-proliferative effect on cells expressing low-affinity (or no-affinity) somatostatin receptor subtypes. It may be possible, through minor modifications in analogue structure, to increase receptor binding and increase anti-proliferative activity, which raises the exciting possibility of generating specific analogues for specific malignancies.

Hepatic reticulo-endothelial system

The hepatic reticulo-endothelial system is an important part of the body's natural defence against malignant cells in the liver. Kupffer cells, the main component of this hepatic system, can kill malignant cells both *in vitro* and *in vivo*. Octreotide has a well documented stimulatory effect on hepatic and splenic reticulo-endothelial activity in both normal and tumour-bearing rats and in cirrhotic patients.[18–20] Indeed, octreotide is more potent than many other well known reticulo-endothelial system stimulators such as glucan and zymosan.[21] Clearly, stimulation of hepatic reticulo-endothelial activity by octreotide could be an important mechanism whereby the analogue inhibits the growth of liver tumours. Nott *et al.*[7] showed a 300% increase in hepatic reticulo-endothelial activity in rats treated with octreotide following intraportal inoculation of tumour cells. Similarly, we have shown a significant effect of octreotide on hepatic reticulo-endothelial activity in rats with hepatic tumours.[20] Furthermore, we have demonstrated that while blockade of the reticulo-endothelial system with gadolinium chloride increased hepatic tumour growth in rats, octreotide was still able to exert a significant but reduced effect on the growth of liver tumours (Figure 1). These observations suggest that stimulation of the reticulo-endothelial system by octreotide may

have a supplementary effect on the action of the analogue in the inhibition of liver tumour growth.

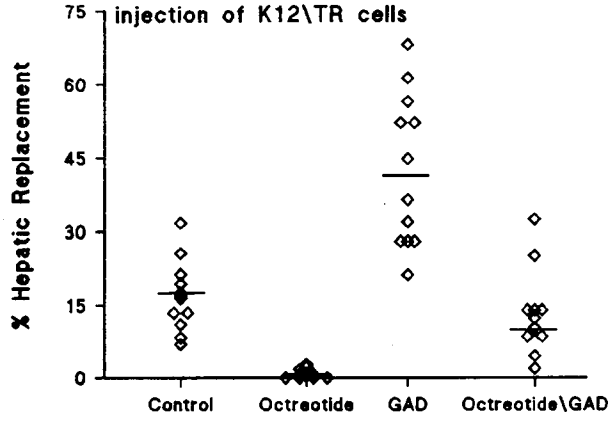

Figure 1. Percentage hepatic replacement (—, median) of liver by K12Tr tumour in rats following blockade of the reticulo-endothelial system by gadolinium chloride (GAD) and treatment with octreotide. Blockade of the reticulo-endothelial system increased the percentage of hepatic replacement compared to control rats. Octreotide reduced hepatic replacement but was more effective in the absence of gadolinium chloride. There were 10 rats in each treatment group.

Octreotide and RC160 have also been demonstrated to reduce tumour growth in the livers of athymic nude mice.[10,11] There is evidence to suggest that the hepatic reticulo-endothelial system components are active and more potent in athymic rats than in euthymic rats.[22] Therefore, stimulation of hepatic reticulo-endothelial activity by octreotide (or RC160) in nude mice cannot be excluded as a possible explanation for the inhibition of tumour growth by the analogue. Reticulo-endothelial system activity is decreased following both anaesthesia and surgery. It may be that a reduction in the hepatic activity of this system at the time of resection of a primary colorectal tumour contributes to the growth of micro-metastases in the liver and allows them to develop into overt tumours. Clearly, a stimulatory effect on hepatic reticulo-endothelial activity in the immediate postoperative period could have potential benefits in the treatment of liver metastases, and we are currently investigating the effects of octreotide on reticulo-endothelial activity following surgery.

Effects on hepatic haemodynamics

Metastatic tumours in the liver receive their blood supply and thus the nutrients required for growth almost exclusively from the hepatic artery.[23] Mechanical interruption of the blood supply by either hepatic artery ligation or embolization results in fewer temporary reductions in tumour growth.[24] The effects of octreotide on hepatic haemodynamics in cirrhotic patients and experimental animals is well documented, the analogue reducing portal venous flow, portal pressure and hepatic arterial flow.[25] The effects of octreotide on hepatic haemodynamics in non-cirrhotic patients and experimental animals is more variable, but generally there is a decrease in liver blood flow. Clearly, any sustained reduction in the blood flow to a hepatic tumour could have an important effect on its growth.

In the study by Notts and colleagues[7] on the effects of octreotide on the growth of Walker cells in the liver, portal venous inflow was reduced in tumour-bearing animals treated with the analogue. In rats with HSN liver tumours, octreotide infusion resulted in a marked decrease in hepatic arterial blood flow.[26] Tumour blood flow was also decreased by octreotide infusion, although this was not statistically significant.[26] On the basis of these observations the authors suggested that octreotide infusion may potentiate the delivery of concomitantly injected cytotoxic agents to hepatic tumours. It was also suggested that octreotide may inhibit tumour growth by reducing its blood supply and hence the supply of nutrients. We have recently demonstrated a significant reduction in blood flow to liver tumours following an infusion of octreotide in rats with WB2054M tumours. However, in rats with K12Tr-derived hepatic tumours, no change in blood flow was observed after octreotide infusion.[27] In both these experiments no significant fall in hepatic arterial or portal venous flow were demonstrated. The slightly divergent results on the effects of octreotide on tumour blood flow may be related to the vascularity of the tumour. Consequently, the more vascular the hepatic tumours the greater may be the effect of octreotide on tumour blood flow.

Effects on angiogenesis

The ability of metastatic cells in the liver to grow into overt tumours depends on their ability to form new blood vessels, a process regulated by a number of angiogenic and growth factors. There is some evidence to suggest that octreotide has an inhibitory effect on angiogenesis. Thus, octreotide has been shown to inhibit the growth of the human breast cancer cell line MCF-7 in animals.[28] The tumours in the octreotide-treated animals were much less vascular than those in untreated mice, suggesting

that the analogue may have an effect on tumour angiogenesis. Similarly, using the chorioallantoic membrane of the chick embryo as a semi-quantative bioassay of angiogeneic activity, octreotide was shown to inhibit angiogenesis in a dose-related manner.[29] Furthermore, octreotide in combination with endothelial growth factor inhibits blood vessel growth.[30]

A recent study by Reubi *et al.*[31] demonstrated a high concentration of somatostatin receptors in the veins located in the immediate vicinity of some human tumours. Although there was some variability in the expression of somatostatin receptors between different types of neoplasms, the most impressive receptor density was observed in veins surrounding colonic tumours, although many of the cancers were themselves somatostatin receptor-negative. Consequently, it follows that the expression of somatostatin receptors in veins is not related to the expression of somatostatin receptors in the tumour itself. No such somatostatin receptors were found in the veins of normal colonic tissue. The authors suggested a number of possible functions for the receptors located in the peritumoural vessels. First, somatostatin may promote a strong vasoconstriction of the peritumoural vessels, which may prevent tumour dissemination. Second, they suggested that the high receptor density may be a host defence mechanism to prevent tumour angiogenesis. Finally, somatostatin could possibly regulate peritumoural inflammation and tissue repair. Clearly, these effects could be important in tumour progression and may be important in the action of octreotide in inhibiting their growth and development. The effect of octreotide on angiogenesis in liver metastases and, indeed, on the expression of somatostatin receptors in the vessels supplying hepatic tumours requires further investigation.

Clinical studies on the treatment of hepatic metastases with octreotide

Octreotide as adjuvant following surgical resection for liver tumours

The only curative treatment for liver metastases remains surgical resection. Only a small number of patients are suitable for such treatment, and in these, recurrent tumours in the remaining liver remain a significant problem. There is evidence to suggest that tumour growth in the regenerating liver is particularly rapid.[32] Possibly, the burst of mitogenic activity that facilitates liver regeneration following partial hepatectomy also potentiates the rapid growth of any remaining tumour cells. We have clearly demonstrated that the growth of both HSN and K12Tr cells in the liver is increased following partial hepatectomy in the rat.[33] However, octreotide significantly inhibited the growth of liver tumours in the regenerating liver. These observations suggest that octreotide may be useful as an adjuvant following the resection of liver tumours. Incidentally, although octreotide also has an inhibitory effect on liver regeneration in the rat,[34] no harmful effects on liver regeneration have been noticed in patients treated with the analogue during extensive hepatic resection for tumours.

Advanced metastatic disease

At present, the only clinical studies of octreotide in the treatment of hepatic metastases have been carried out on patients with advanced metastatic disease. Only in those patients with hepatic metastases derived from gastro-intestinal endocrine tumours has there been any proven tumour regression and prolonged symptomatic relief.[3] The results of studies on the treatment of patients with advanced colon cancer have largely been disappointing. Thus, in one study, 12 patients with advanced colon cancer, 10 of whom had liver metastases, were treated with 150 μg octreotide subcutaneously three times a day until the disease progressed.[35] Although the octreotide therapy was generally well tolerated, no significant regression in tumour size was observed in any of the patients. Six patients showed evidence of disease progression 3 months after commencing octreotide therapy and six patients had stable disease, although all eventually progressed. The patients included in this study all had extensive disease with poor performance status, and no significant response to octreotide treatment was observed.

Similarly, Klijn *et al.*[36] treated 34 patients with metastatic gastrointestinal tumours with octreotide (16 colorectal, 14 pancreatic and four gastric) and of these, 22 had liver metastases. Octreotide was given by subcutaneous injection, starting at 100 μg three times a day for the first week and then increasing to 200 μg three times a day. Again, the octreotide was generally well tolerated, although one patient developed severe oesophagitis accompanied by a decreased mobility of the distal oesophagus. No complete or partial response to octreotide was observed in any of the patients. In eight

patients the disease was observed to be stable (four with colorectal, three with pancreatic and one with gastric cancer), whereas in the others the disease progressed despite treatment with octreotide. However, most patients experienced a temporary subjective improvement to octreotide therapy with a decrease in pain.

Pancreatic cancer

Octreotide and other somatostatin analogues have a significant inhibitory effect on the growth of pancreatic cancer cell lines both *in vitro* and *in vivo*[3] and there was some optimism that this effect may be reproduced in patients with pancreatic cancer. The effect of octreotide on advanced pancreatic cancer has been investigated in at least two studies.

Friess *et al.*[37] treated 22 patients with advanced pancreatic cancer with octreotide 100 μg three times a day, increasing to 200 μg if the disease progressed. No patient tumour response to octreotide therapy was observed in any patient and none derived any symptomatic benefit. In those patients with stable disease, the lack of any response was thought to relate to tumour stage rather than octreotide therapy.

Ebert *et al.*[38] compared the effect of low- and high-dose octreotide in patients with advanced pancreatic cancer, some of whom had liver metastases. Twenty-two patients were treated with 100 μg octreotide three times a day and 12 with 2000 μg three times a day. In the low-dose group, the median survival was 4 months and no complete or partial remission or symptomatic benefit was observed. In the high-dose group, the median survival was 6 months, while four patients showed evidence of stable disease for more than 3 months during octreotide therapy but the remainder progressed despite treatment. Symptomatic improvements were seen in four patients. Even at this high dose, octreotide was well tolerated, the only adverse effects being steatorrhoea in 25% and mild hyperglycaemia in 60% of patients. The authors concluded that given the advanced stage of disease in their patients, the results of high-dose octreotide treatment were promising.

Conclusions

Overall the results of the clinical trials of octreotide in advanced malignancy are poor. At best, the disease remains stable but as yet no objective tumour response has been reported. There has been evidence of some symptomatic improvement in some patients treated with octreotide but this may have more to do with the analgesic effects of the analogue or its beneficial effects on malignant bowel obstruction.[39] In addition, the incidence of serious or unpleasant side effects associated with octreotide therapy in patients with advanced gastrointestinal malignancy is very low. It is perhaps not surprising that octreotide has little effect in advanced metastatic disease since its cytostatic and anti-proliferative or inhibitory effects are unlikely to be beneficial in the presence of such a massive tumour burden. The promising effects of a high-dose regimen in patients with advanced disease[38] leaves ground for some cautious optimism and future trials should concentrate on high-dose treatment.

Furthermore, since octreotide and somatostatin are cytoprotective in the liver, concomitant administration of cytotoxics with the analogue may improve the response rates and at the same time protect the liver from the hepatotoxic effects of the chemotherapeutic agents.[40,41]

If octreotide is to have a role in the treatment of liver metastases it is likely to be most beneficial when the tumour burden is relatively small. Our studies and those of others have shown that octreotide can inhibit the growth of established micro-metastases in rats. If this effect can be reproduced in patients then octreotide should be useful as an adjuvant following surgery, particularly following the resection of primary colorectal cancer. The stimulatory effect of octreotide on hepatic reticulo-endothelial system activity may be particularly beneficial in the postoperative period in restoring and increasing Kupffer cell activity which is reduced by both surgical and anaesthetic trauma and the presence of malignancy. Levamisole in combination with 5-fluorouracil is effective as an adjuvant in colorectal cancer.[1] Levamisole is an immunomodulator and this effect may explain its beneficial effect when used in combination with 5-fluorouracil after surgical resection of colorectal tumours. Although levamisole can stimulate hepatic reticulo-endothelial system activity in rats, octreotide is significantly more potent in this respect.[21] The potential role of octreotide combined with chemotherapy has not been investigated either clinically or experimentally.

Octreotide has well documented inhibitory effects on the growth of many animal and human cell lines, including colorectal cell lines both *in vitro* and *in vivo*. Colorectal cancer metastatic to the liver

is clinically important both in terms of the number of patients affected and the lack of any effective treatment for the majority of patients. Octreotide inhibits the growth of colorectal liver tumours in a number of experimental models and, in at least three tumour types, inhibits the growth of established micro-metastases. The precise mechanism of action of octreotide in inhibiting the growth of liver metastases is not known, Further investigations on both receptor-mediated and receptor-independent anti-proliferation are needed. The effects of octreotide on hepatic reticulo-endothelial system activity and hepatic haemodynamics also require further clarification. The effects of octreotide on angiogenesis are interesting and could also be an important mechanism whereby the analogue inhibits the growth of liver tumours. Octreotide inhibits the growth of tumours in the regenerating liver and this suggests that the analogue may have a beneficial effect in reducing liver tumour recurrence following hepatic resection for liver metastases. Octreotide is unlikely to be effective in the treatment of advanced metastatic disease but its use in the treatment of more limited liver metastases needs further investigation.

We believe that the available evidence, although experimental, suggests that octreotide may have a beneficial effect on the development of liver metastases when used as an adjuvant to surgery in colorectal cancer and this area warrants urgent clinical investigation. The cytotoxics which are currently used as an adjuvant to surgery for colorectal cancer have unpleasant side effects which can be life-threatening. There will also be a proportion of patients who have undergone a truly curative resection of their tumour and will thus be treated unnecessarily. The potential benefits of octreotide in the adjuvant setting, although promising, remain speculative, but in its favour octreotide has an acceptably low incidence of side effects and can be administered safely for a prolonged period of time.

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