Preface

Despite the enormous advances in science and medical technology in recent times, our knowledge of the pathophysiology and treatment of neoplasia is far from complete and, for the patients at least, the myths that surround cancer remain intact. Cancer remains the 'bogy man' of medicine as we enter the new millennium, and the very mention of the word strikes mortal fear in patients and their families in a way not generally seen with any other disease.

Although chemotherapy is very effective in the management of certain neoplasms such as testicular cancer, the efficacy of this therapeutic modality in the treatment of many common malignancies such as those of the lung, breast, prostate, bowel, pancreas and kidney is limited. Cure of macroscopic metastatic disease is exceedingly rare, and palliation of symptoms of metastatic neoplasms by chemotherapy can be problematic since the toxicity of the treatment often outweighs any improvement in quality of life resulting from a temporary decrease in tumor burden. This situation has not only motivated attempts to develop novel cytotoxic agents and targeted chemotherapy, but has also stimulated research on innovative noncytotoxic therapies for cancer.

Amongst the various hormonal agents, currently being evaluated for the management of neoplasia, considerable attention is directed to somatostatin analogs. This is largely due to the demonstration of antineoplastic activity of these compounds in a variety of experimental models in vitro and in vivo and to the elucidation of some aspects of the molecular mechanisms whereby they exert their cytostatic and cytotoxic effects. Furthermore, clinical experience with somatostatin analogs in the treatment of conditions such as acromegaly and GEP tumors has shown that they are well tolerated compared to other antineoplastic therapies currently in use. As a consequence, there is much ongoing clinical research to determine whether or not results from experimental studies will translate into clinically useful antineoplastic activity.

In the recent years there has been extensive international media coverage of the allegedly successful treatment of a number of malignant neoplasms with the Di Bella multitherapy (DBM). This is a multidrug, individually tailored medical treatment (comprising a mixture of melatonin, bromocriptine, somatostatin, a solution of retinoids, and, depending on the kind of cancer, either cyclophosphamide or hydroxyurea) developed by Luigi

Di Bella, an Italian physician. Over the past 25 years Dr. Di Bella has consistently used it on an outpatient basis claiming its effectiveness in halting the progression or completely curing most cancers. Not surprisingly, in view of the public interest in cancer therapy, a number of associations have been formed to support this treatment. As a matter of fact, these associations mounted a campaign to request that DBM be included among those cancer treatments considered to be effective and that its cost be fully reimbursed by the Italian National Health Service. Despite some debate about the methodology of the different clinical trials [1–8], a phase II study, coordinated by the Italian National Institute of Health and the National Cancer Advisory Committee, did not show sufficient efficacy in patients with *advanced cancer* to warrant further clinical testing [9]. Furthermore, a follow-up of treated patients did not give any evidence that DBM improves the survival of cancer patients [10].

Since somatostatin or octreotide represent only one component of the DBM, the ineffectiveness of this approach does not necessarily translate into a lack of efficacy of peptide analogs in the management of neoplasia. A single component of a multidrug therapy could indeed be effective on its own [11]. However, as summarized by Jenkins et al. [12] in this issue, apart from some notable exceptions, somatostatin analog therapy has proven to be disappointing in the management of *advanced malignancy*. Should somatostatin analogs be abandoned? A thorough analysis of the available literature suggests that this is not the case. Indeed, besides being used in cancer treatment (alone or in combination with other cytotoxic or hormonal agents) and palliation, radiolabelled somatostatin analogs are employed for the localization of primary and metastatic tumors expressing somatostatin receptors. Indeed the so-called ‘somatostatin re-

ceptor scintigraphy’ is the most important clinical diagnostic investigation for patients with suspected neuroendocrine tumors. Targeted radiotherapy, which is being evaluated in clinical trials, represents an obvious extension of somatostatin scintigraphy. In addition, new receptor-selective and ‘universal’ analogs are being developed and new high-dose regimens are being tested. Further, somatostatin receptor-targeted chemotherapy represents an appealing approach to treatment of SSSTR-expressing tumors. Finally, the genetic transfer of hSSSTR-2 and hSSSTR-5 genes together with the genes that encode their membrane proteins to those neoplasms that do not express these receptor subtypes will translate the benefits of gene therapy to somatostatin analogue treatment of cancer. The final chapter on somatostatin and cancer has, therefore, not yet been written.

Taking all the above considerations into account, we felt it timely and worthwhile to attempt a *critical* review of the recent developments in the field. To this end, the present issue of *Chemotherapy* was planned with the aim of synthesizing the massive body of evidence available on somatostatin analog therapy of cancer and the scientific basis for their antineoplastic effects, to enable oncologists to rationalize the use of these compounds in their clinical practice and to stimulate research on new therapeutic approaches.

Unlike some other publications in the field, this supplement is not the result of any national or international symposium. It represents the collection of 11 commissioned monographic reviews generously offered by 30 international scientists, all of whom have significantly contributed to this new knowledge, in order to provide a glimpse of what may lie ahead. I am indebted to all the contributors for having accepted to share with us their experience of somatostatin analog therapy of cancer and for providing us with excel-

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