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GUEST EDITORIAL

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The use of systemic enzyme therapy in oncology

This issue of *Cancer Chemotherapy and Pharmacology* contains peer-reviewed articles, the results of which have been presented at international meetings, most of them at ECCO 10, Vienna, 12–16 September 1999. During the latter half of the 20th century, there was exceptional progress in the fight against cancer. Many types of cancer particularly those affecting children, are nowadays curable diseases. Some haematological and solid tumours which occur in adults are also now curable. However, despite decades of basic and clinical research, and trials of promising new therapies, solid tumours remain a major cause of morbidity and mortality. Our modest clinical successes do not reveal the extent of the advances in understanding the biology of cancer. Whilst it is difficult to predict which element of research will have a positive clinical impact in the 21st century, it would be reasonable to expect further success.

The three main aims of treatment of patients with cancer are clinical cure, improvement of quality of life and prolongation of survival. The concept of clinical cure requires that a group of long-term survivors shall not have a higher risk of dying from cancer of the type for which they were originally treated than persons of the same age and sex in the general population. Demonstration of clinical cure relies therefore on information about individual causes of survival or death in long-term follow-up studies. Any treated cancer patient who dies from other causes without any signs or symptoms of his original cancer is a demonstration of individual cure. Today, considerable emphasis is placed upon clinical effectiveness of a treatment and the statistical proof of clinical cure. Such proof of efficacy may be very elusive in some cases where for many patients the length of recurrence-free survival without morbidity may be foremost in their mind. New methods of treatment that can prolong this time will have the effect of increasing the number of 'cured' patients since, epidemiologically speaking, they will on average, have been exposed for a longer period of time to the competing risks of death from other causes.

In order to observe an increase in the number of 'cured' patients alternative methods of assessing the efficacy of treatments need to be developed which take into account the influence of natural modulators of cell growth and invasiveness, which influence the growth and spread of cancer. Schneider (Hannover) introduces in his guest editorial a statistical tool – the method of epidemiological retrolective cohort studies – which allows the researcher to determine the therapeutic potential of biological response modifiers and their relationship to existing therapy modalities. A scientific approach to assessing therapeutic benefit from this form of combination therapy is essential especially where it is used alongside cytotoxic agents and radiotherapy in the overall management of advanced cancers. Such an approach is also justified in view of the lack of progress observed in increasing the effectiveness of chemotherapy and radiotherapy in the treatment of systemic disease and localized tumours, respectively.

The clinical trial concept of a therapy-optimizing study is a promising tool that combines effectively already approved and active treatment regimens with new agents to the benefit of patients. Agents selected for therapy-optimizing studies should be synergistic with the medications detailed in the approved clinical protocol with respect to tumour response, and quality and prolongation of life. The substance should not cause any side effects either alone or in combination with other therapeutic agents nor interfere with the other agents specified in the original protocol.

Clearly, it is a prerequisite that agents selected for use in therapy-optimizing studies should be evaluated for their pharmacological and pharmacodynamic activity in

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order to identify their mode of action and subsequently a rationale for their use. The use of oral enzymes in oncology either as an adjuvant or as an additive therapy has been disputed. Supporters of chemotherapy have in the past paid little attention to this additional treatment option due to the absence of convincing clinical data. But that is about to change. In an age in which medical science is increasingly specialized we should remind ourselves that many approved drugs are based on naturally occurring compounds.

Enzymes are molecular saboteurs. They exert their effects by gumming up the works of key proteins in the body. They drop their wrenches selectively, slotting seamlessly onto binding domains of their target proteins, cleaving them into peptide fragments and leaving other proteins untouched. It was in 1926 when Sumner crystallized the enzyme urease from jack bean meal and identified it unequivocally as a protein. He ultimately was awarded a Nobel prize for his efforts and at present, enzymology occupies a very important position in medical, biological and industrial research.

Enzyme therapy modalities have found their way into oncology, e.g. asparaginase which cleaves asparagine into aspartic acid and ammonia disrupts the supply to lymphatic leukaemia cells of this essential amino acid, and hyaluronidase which may improve the transport of cytotoxic drugs to, or facilitate the oxygen level in, tumour tissue by degradation of the extracellular matrix or alteration of the central tumour interstitial fluid pressure, respectively.

The original articles published in this edition of *Cancer Chemotherapy and Pharmacology* provide the scientific community with data from in vitro animal and clinical studies to confirm the efficacy of enzymes used in therapy-optimizing studies. The issue starts with a paper by G. Birkenmeier et al. (Leipzig) on the modulation of growth factor binding properties of α2-macroglobulin by enzyme therapy. These authors showed using biochemical approaches that the intestinal absorption of proteinases triggers the formation of TGFβ-binding species of activated α2-macroglobulin by converting this clearance protein from the so-called 'slow form' into the 'fast form'. High concentrations of TGFβ, chemokines and cytokines, as reported by other workers, are preferentially bound leading to increased clearance in the form of the α2-macroglobulin-cytokine complex. Thus, proteinase therapy, using trypsin, chymotrypsin, papain or bromelain may prove beneficial in patients with certain cancers by reducing the level of growth factors which are known to be elevated in such patients.

Desser et al. (Vienna) have shown that oral therapy with proteolytic enzymes decreases elevated TGFβ levels in the blood of volunteers given orally low dosages of a cocktail of active proteinases over a period of 7 days. The paper by Wald et al. (Prague) extends the molecular results on cytokines at the cellular level. His group was able to demonstrate in a mouse model using syngenous melanoma B16 cells that a mixture of enzymes reduces formation of metastases and extends survival time of the treated mice. They also report a decreased expression of CD44 and CD54 molecules in tumours exposed to proteolytic enzymes and conclude that serine and cysteine proteinases are able to inhibit metastatogenesis.

Further evidence of surface protein modulation by proteolytic enzymes is given by the work of Zavadova (Prague) and Freedman (Houston) using dendritic cells from the peritoneal cavity and peripheral blood of ovarian cancer patients. They cultured these professional antigen-presenting cells in the presence of polyenzyme preparations and were able to induce enhanced maturation. These results will be published in *Cancer Chemotherapy Pharmacology* Vol. 48, issue 3.

The following two papers deal with the reduction of side effects of radiotherapy treatment with oral enzymes in patients with head and neck and uterine cervix cancer. Gujral et al. (India) were able to demonstrate an alleviation of acute side effects, e.g. mucositis, skin reaction and dysphagia, following radiation therapy in head and neck cancer patients (stage T3/T4). In this prospective, randomized but open study the patients received an oral proteolytic enzyme preparation during conventional fractionated radiation therapy. Dale et al. (India) carried out a prospective, randomized, open clinical trial in patients with locally advanced carcinoma of the uterine cervix and monitored skin reactions, vaginal mucosal reactions, genitourinary symptoms and gastrointestinal reactions during radiotherapy and intracavity brachytherapy. Patients assigned to the test group received additional oral proteolytic enzyme treatment and experienced a significant reduction in radiotherapy-related side effects.

The next three clinical papers deal with epidemiological retrolective cohort studies, the basic features and rationale for which are given by Schneider (Hannover) in his editorial. Sakalová et al. (Bratislava) provide evidence that an additive therapy of oral enzymes, integral within a conventional multidrug protocol for multiple myeloma stage I–III, results in significantly higher overall response rates and longer duration of remissions than any reported to date. These encouraging clinical results have prompted the United States Food and Drug Administration (FDA) to grant an Orphan Drug Status to oral enzymes. These results may be confirmed by the results from a multicentre, randomized, double-blind, placebo-controlled, prospective trial in stage II multiple myeloma patients, currently underway in the US investigating the combination of melphalan/prednisolone and proteolytic enzymes.

Epidemiological multicentre retrolective cohort analyses of therapeutic data obtained from breast and colorectal patients are reported in the last two papers. Beuth et al. (Cologne) examined patients with breast cancer ranked at all levels on the UICC scale, who underwent the standard programme of treatment. The study included both patients who had received no additional therapy and those that had received other forms of aftercare (e.g. physical therapy, phytoextracts or organic extracts, trace elements or vitamins), or

additional oral enzyme therapy. The retrolective cohort analysis revealed that patients receiving oral enzyme therapy, showed an improved quality of life due to the early and continuous relief from the side effects of conventional therapy. Preliminary data suggest that oral enzymes may prolong the survival of patients. A similar analysis in patients with colorectal cancer by Popiela et al. (Cracow) resulted in almost identical conclusions. These authors analysed the survival time for the total patient sample by Kaplan-Meier analysis, adjusted for demographic, risk and therapy criteria. In patients with disease stage Dukes D taking oral enzyme therapy, a distinct effect on median survival time was shown by explorative analysis. The results of these two retrolective studies need to be confirmed by prospective, randomized, double-blind studies before further decisions can be made; a study in breast cancer patients is at the initiation stage. A study in colorectal patients is already ongoing with the surgical oncology group of Popiela (Cracow). These studies may indicate whether or not the book on additive oral enzyme therapy should be closed.

There is no doubt that further advances in molecular biology in the field of cancer treatment will allow us to understand more fully how and why a drug works, and this holds true in the clinical use of enzymes. In experimental settings, it has been shown that proteolytic enzymes are active substances in the fight against malignant cells, and in addition successful animal models have been established to elucidate the mode of action of enzymes in the process of metastasis formation. The route from the bench to the ward is, however, laborious and time-consuming and protagonists of oral enzyme therapy should be allowed time to present robust clinical data that warrant attention from oncologists that oral enzyme therapy is indeed an additional treatment option when combined with conventional therapy programmes.

The trial and error approach, by which medicines have been discovered over the past 100 years is still ongoing at the beginning of the 21st century. However, the more we are armed with the blueprints for genes of enzymes of interest, the more we can effectively develop individually designed enzymes. Experimental work with such 'designer enzymes' is currently underway focusing on ways in which tumour cells may be compromised through the cleavage of key proteins, essential for cell proliferation and invasion.

This series of peer-reviewed articles from the laboratory to clinical studies presented in this special edition of *Cancer Chemotherapy and Pharmacology* represents a syllabus of oral enzyme therapy. This body of work should be seen as a database for critical review and further discussion within the scientific community on the clinical value, risk-benefit and social and economic benefit of oral enzyme therapy and its integration into conventional treatment programmes.