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Summary. Medical oncology is now accepted in Europe as a branch both of internal medicine and of clinical oncology. In this article the present situation of this discipline is analysed with reference to the plateau in the results achieved in chemosensitive tumours and to the small effect of chemotherapy in tumours considered to be "big killers". Although new avenues in tumour biology do not necessarily mean therapeutic success in the near future, at present basic discoveries are being developed for clinical therapy faster than before. Besides biological response modifiers, the development of new drugs should receive constant attention from medical oncologists. This attitude has persisted despite an awareness that the political community has had little interest in the allocation of funds for the development of new anticancer agents. Clinical trials have recently been subjected to some criticism. But unless large multicentre trials are continued with better quality control and organization it will not be possible to provide adequate resources for the many and various new drugs and biological response modifiers expected to enter the field in the next few years. The active involvement of medical oncologists in controlled clinical trials should then continue. Finally, the task and achievements of the scientific society, which allows close contacts among European medical oncologists, are briefly underlined.

Introduction

Since it was first defined in the 1970s, medical oncology has been progressively encroaching on various areas of research and clinical practice. It is worth bearing in mind that medical oncology is a branch both of internal medicine and of clinical oncology, dealing therefore with the medical aspects of neoplasia; this means skill in the use of anticancer chemotherapy agents, in the endocrine therapy of tumours and in the immunological approaches to the treatment of cancer. The best definition of medical oncology is perhaps the French one: "médecine interne cancérologique".

Divisions and departments of medical oncology were first initiated in the United States, and later also in Europe, primarily in France. If we try to summarize the current activities of medical oncologists, the main fields of present research activity in medical oncology are as follows: phase 1 and 2 studies, and also phase 3 studies (the clinical activity of new agents can be studied in single institutions or on a multi-institution basis); studies of new modalities of treatment, such as bone-marrow transplantation and intra-arterial chemotherapy, which are also carried out on a single institution basis; and supportive therapy and quality of life. With the possible exception of the studies on intra-arterial chemotherapy, it is now generally accepted that all these areas can be dealt with by medical oncologists, which means that the role of medical oncology has been widely accepted at least in the oncological community.

Yet, in spite of some brilliant prospects, why does there seem to be a smouldering crisis in medical oncology? Some specialists working in other branches (radiotherapists, surgical oncologists) have also been going through a similar crisis with no real new solution emerging. In the case of medical oncology, however, we think that this crisis is barely apparent; some degree of disappointment comes from having reached a plateau in the results achieved in chemosensitive tumours and from the small effect of chemotherapy in solid tumours considered to be big killers, e.g. those in lung, stomach and colon. Some frustration stemming from the lack of results is present even among medical oncologists involved in new drug development and in clinical research activities. The development of new analogues of antitumour drugs, which initially seemed so promising, has not really provided a new drug that can offer a true advantage over its parent compound, in spite of the expensive studies pursued in a variety of solid tumours. This subtle melaise, in spite of some definitely brilliant prospects coming from tumour biology, comes from the awareness of the astute medical oncologist that new avenues in cancer cell biology do not automatically mean a therapeutic success in the near future.

Nevertheless, this revolution in basic research aimed at the availability of new biotechnology products has perhaps not been followed through with enough attention by medical oncologists. Often the work in the field of clinical research on biological response modifiers (interleukins, retinoids) has been carried out by clinical specialists other than medical oncologists, such as surgeons or radiotherapists. This has a positive aspect, since it shows that in the field of clinical activity other specialists are also curious and open to new ideas, but it is a pity that medical oncologists have been missing out on a new aspect of something that should be dealt with within the discipline. We must recognize, however, that interest in some of the fields of activity within the discipline, such as the diagnostic ap-

proach and the natural history of some neoplasms has been declining. One consequence of this is that staging procedures have not been receiving much attention in the last few years. There are exceptions, however: for example, the application of monoclonal antibodies to the classification of haematological malignancies. Nonetheless, some aspects of the natural history of neoplasms are still interesting from a research point of view, and two examples in particular should be borne in mind. The first issue, in our opinion, is that of the neoplastic complications of AIDS. This is a new biological and therapeutic problem, which concerns the medical oncologist as well as other specialists. The second issue is the problem of tumours in the elderly; the median age of the European population is increasing, and the problems of the elderly therefore need more attention.

The neoplastic complications of AIDS are now related to major health problems in Europe, having extended from the USA to the nations of Europe. In this field, prevention, especially in young patients, has a most important role to play, and it is obvious that further insight into the aetiology and pathogenesis of the neoplasms concerned may be provided. We think the term "neoplastic complications of AIDS" is perfectly appropriate. In Italy over 50 cases of malignant lymphoma, mainly non-Hodgkin's lymphomas and Hodgkin's lymphomas, have been found in patients with or at risk for AIDS. Kaposi's sarcoma has also been associated with AIDS and AIDS-related syndrome in this country. But we are aware that the same problem is present in France, England, Germany, Switzerland and Spain, and also in the Scandinavian countries. A registry of neoplastic complications of AIDS is needed and is already in the planning stage; to the EORTC has been proposed a registry of these cases, for use in attempts to prevent AIDS and for a planned therapeutic approach to the neoplastic complications of AIDS. Medical oncologists should be in the front line of this programme, as they have been in the United States.

Tumours in the elderly are the second problem relating to the natural history of tumours that should be receiving the attention of active researchers in the field of medical oncology. Too often we miss the fact that around 50% of tumours develop in people over 60 years of age and around 30% in people around 70 years of age and that the median age of the population is increasing in Europe. Faced with this situation, we should recognize that in too many instances there are no appropriate therapeutic protocols; most of these patients are in fact excluded from the current protocols after the age of 70, and too often they run the risk of under- or overtreatment, which can mean toxic death. We therefore need a new approach to the treatment of tumours in the elderly and new methodology, and we must be able to exploit the therapeutic potential available to the maximum.

Clinical trials in the future

Are clinical trials still important? In the last few years there has been much debate on this subject. In his article "Some Thoughts on the Future of Clinical Trials", Wittes [27] concludes that clinical trials, and especially multicentre clinical trials, are still essential for the development of better therapies. The reason for this assertion is that if the size of clinical trials is limited they will probably not be able to provide an adequate resource for the testing of the very large number of new drugs and biological response modifiers expected to enter the field in the next few years unless multicentre trials are continued and unless the new ways to set other priorities are found. We shall, however, be able to improve our skill in the conduct of clinical trials, which will probably require changes in the methods used hitherto. We need larger studies; small studies are a waste of time and we must settle for fewer trials. The number of intergroup activities will have to be increased, but this is not enough; the administrative mechanism will have to be more efficient and simpler, and better guidelines for fewer reviews are needed. A further basic requirement is an equitable distribution of responsibilities for protocol formulation and scientific credit [27]. Reflections on cooperative groups, such as the Early Clinical Trials Group of the EORTC, have been made by Pierre Dodion, who has also made some general recommendations (1986, personal communication) deserving of mention (together with the recommendations of the editorial board of Cancer and Cancer Treatment Report): the study should not have unavailability for measure end points of greater than 15%. No more than 15% of eligible patients should be lost to follow-up or considered unevaluable due to early death, protocol violation, missing information, etc. A quality control review of the ECGT data has been advised, as a means of finding how their performance might be improved. Dodion recommends, among other things, that more randomized studies should be performed and that registration should be associated with a check of eligibility criteria: computer use allows a quick control of the main eligibility parameters (age, performance status, trial therapy, biological values, measurable lesions, etc.). Registration and randomization would be refused for ineligible patients. Sanctions, even economic sanctions, should be applied for inappropriate information at registration. A better way of avoiding data omissions would be for the principal investigator to telephone (mail may sometimes be ineffective) the appropriate institution: person-to-person conversation allows quicker recovery of missing data, and more detailed information may be obtained. Gaps in the data should be detected rapidly by principal investigators in order for action to be efficient; probably a physician should be present in the data centre to allow a rapid check on these problems. These thoughts are mentioned as a result of several years' experience of ECTG clinical trials.

We believe that there is a better way of running clinical trials; they are still necessary and useful for data collection as well as for patients. A secondary effect of clinical trials is an improvement in the quality of care given to the patients, and we must also be aware of that. However, again, an improvement in our performance is necessary. To attain this goal, quality control of our work is essential, and for this reason site visits once a year or every 2 years to each centre participating in a co-operative study, or more frequently in centres with problems, might be advisable.

New leads from biology for medical oncology

We are living in an era where basic discoveries in the field of cancer biology are resulting in products faster than ever before by biotechnology companies. Too often, however, industry is leading the way [11] rather than government (and rahter than basic research people in our institutes).

We should be aware that new leads from tumour biology and preclinical development therapy promise possibilities that could not have been envisioned a few years ago [19]. This has been understood very well by the pharmaceutical industry, but not always sufficiently well by all medical oncologists. I will only mention some such areas of possible and future application. One is that of the cell differentiation inducers (e.g. methylformamide, azacytidine and retinoic acid). Another new avenue is the use of monoclonal antibodies conjugated to plant toxins, toxic drugs and the isotopes: some of these have been shown to be active in human tumour xenographs. Another promising area is that of the modulation effect on immunocompetent cells, for example through interleukin 2 and interferons. Interferons themselves are excellent examples, since they have a multiple mechanism of action: an antiproliferative activity which is one of their properties, also coupled with immunomodulation activity, cell differentiation and increase in cell surface antigen expression [10]. The clinical activity of interferon has been detected in hairy cell leukaemia, but this biological response modifier has also shown activity in melanoma, renal cell carcinoma, Kaposi's sarcoma and myeloma: in these neoplasms there have, in fact, been small but definite responses.

Among the future outlooks on research areas, particular attention should be given, when possible, to the clinical application of growth factors [23]. Experimental approaches are currently being directed at the development of antibodies to growth factors, the development of antibodies to receptors of growth factors [17] and the development of analogues to growth factors. Oncogenes are strongly related to the mechanism of growth regulation [23]: manipulation of the oncogene expression such as can be obtained by the development of anti-oncogenes could lead to the alteration of growth of neoplastic cells. But growth factors do not mean pure theory, some of these are commercially available, for example the porcine platelet-derived growth factor is nowadays produced by the pharmaceutical industry. In this field, as in the field of other biological response modifiers (e.g. tumour necrosis factor), the pharmaceutical industry has been quite active. More than ten pharmaceutical companies are major developers of lymphokines, in addition to which more than ten companies are now major developers of monoclonal antibodies and more than five pharmaceutical companies in the world are major developers and quite active producers of differentiating factors. In an article published in the International Business Week Magazine of September 22, 1986 [11] some "biotech plays on the war against cancer" are well displayed, as is the total capital raised by the several pharmaceutical companies active in the production of interferon, tumour necrosis factors, interleukin and monoclonal antibodies. The total capital raised for each company varies within the range of $ 100 million to $ 300 million. Also, a look at the titles of some of the more recent meetings, such as the NCI-EORTC Symposium held in Amsterdam in October 1986 [19], makes it obvious that early data on toxicity and results are already available in the field of adoptive cellular therapy with lymphokine-activated killer cells plus interleukin [14, 18] and in that of tumour necrosis factor [21]. Furthermore, the clinical use of monoclonal antibodies not only for diagnostic, but also for therapeutic purposes, has already been initiated (e.g. with the use of a monoclonal antimelanoma antibody-ricin A chain immunotoxin) [2, 4, 15, 22]. Another quite interesting area is that of the angiogenesis factor. We all know that this factor is necessary for neoplastic cells to develop. If it were possible to block this factor this would probably have a negative action on neoplastic growth [9].

New anticancer agents

The development of new anticancer agents is an area of present research relying heavily on the activities of the National Cancer Institute. In recent years there has been a swing away from experimental animal tumour models to human cell lines, since the yield of the first approach has not been very rewarding. We need models that are biologically more closely related to human neoplasms: an important aspect of development is the assessment of the activity of new agents in nude mice implanted with human cell tumour lines. In this field of development of new agents, which is closer and more traditional to medical oncology, the activity of the New Drug Development Office in Amsterdam must be underlined, as must that of the Early Clinical Trials Group of the EORTC, which has tested many new drugs in conjunction with the National Cancer Institute in the last few years.

Medical oncologists, like other clinical oncologists, are aware that relevant progress has been achieved through the development of new anticancer agents and that this might continue in the future. We must, however, be aware that the political community has displayed a lack of interest in the expenses needed for the development of new anticancer agents. We think that this is reflected in the new Food and Drug Administration (FDA) requirements for approval of anticancer agents [12]. In the past, new anticaner agents were approved solely on the basis of objective response, but this is no longer the case. Now favourable expected survival time and/or quality of life is generally required for approval, and a minimum of two prospective randomized studies is necessary for assessment of this. The FDA requirements also address the use of combination chemotherapy, and according to these requirements "the combination including the safe drug must be superior to the combination without the safe drug and a substitution of the safe drug for a drug in a combination in comparison with the original unconstituted combination, presents no problem if an advantage is demonstrated, but again this advantage has to be demonstrated on survival or on quality of life". In our opinion, such speculations are too restrictive: even some of the neoplastic agents in current use have not been demonstrated to increase survival singly or in combination. But it is generally accepted that a partial remission can be appreciated by the patient, even without positive effect on duration of survival. The concept of quality of life is a current one, but in our opinion it has still not been well defined. This emphasizes that an improvement in the quality of life is not something that can be easily quantified.

New FDA policies must therefore be considered. Rapid approval is needed for the investigation of new drugs, so that new compounds can be tested sooner than hitherto in patients with metastatic cancer. This is now possible for AIDS, but patients with metastatic cancer are in a similar situation as far as prognosis is concerned: most are likely to die within a short time, as AIDS patients are. The in-

creasingly stringent requirements for the approval of new anticancer agents might discourage the pharmaceutical industry from investment in the field of anticancer drugs and deflect it into other, "easier" areas (e.g. antibiotics or psychotropic drugs). These FDA regulations obviously apply to the United States, but the situation in the United States will have a strong influence on that in Europe. It is useful to have some kind of restriction, because it brings us back to the point we raised in the first part of this presentation with respect to the quality of our trials: we need fewer and better designed trials with definite endpoints. On the other hand, it could slow down the development of new anticancer agents in the future. We believe that the European Society for Medical Oncology (ESMO) should join forces with the American Society for Clinical Oncology on this subject and adequately criticize these new FDA regulations.

Assessment of progress against cancer

In May 1986 Bailar and Smith published an article entitled "Progress Against Cancer?" in the *New England Journal of Medicine* [1]. This paper initiated a wide and critical debate in the same journal [6, 7, 8, 16, 24–26], which is still open. The article was somewhat misleading, since it fails to mention one very interesting aspect of the real progress made against cancer, which emerges when data are considered with reference to the age-specific rate rather than the age-adjusted rate [3]. In Bailar and Smith's the question mark in the title suggests such strong sentiments as a generally dismal picture, deliberate deception, losing the war, qualified failure, after the expenditure of countless billions. Medical oncologists would like to consider measurable facts, and not simply rhetorical words.

From a useful analysis made by Breslow in 1986 of specific cancer mortality rates versus number of cancer deaths per 100000, it emerges quite clearly that the most substantial drop in cancer mortality began around the 1960s for children aged less than 5 years, in the 1970s for persons aged 5–44 years, and since the 1970s for persons aged 45–54 years. Beyond 50 years of age cancer mortality has continued to rise because of a lung cancer epidemic (treatment has never been very effective in lung cancer). Breslow shows that all other cancer mortality than lung cancer mortality has been declining to some extent since the 1950s in the 55–85 age group.

Declining mortality is not the only parameter of progress, however. Every middle-aged medical oncologist, having treated such patients over a number of years, knows what the benefits of a complete remission are to patients with malignant lymphoma or some other neoplasm responding to chemotherapy, even if the patient eventually dies of the disease nonetheless. The use of mortality as the only standard is thus misleading not only from a biological point of view, but also from the point of view of patients benefiting from a response to anticancer therapy. If mortality is considered the only measure of the efficacy of treatment and no substantial progress can be detected, however. I think that failure probably cannot be ascribed solely to inadequate therapy; there have been failures in the areas of early detection and primary prevention. The increase in lung cancer mortality, for example, reflects a failure in the field of primary prevention.

New and old roles of medical oncology

We firmly believe that the traditional role of medical oncology should be maintained. This means continuing with total care of the patients; medical oncologists are primarily specialists in internal medicine who are involved in the care of patients with cancer. Clinical research is of course intrinsic to medical oncology: it is impossible to conceive of a medical oncologist who only applies notions and does not take part in clinical trials. Clinical research, however, should not rule out human relationships with the patient and his family. We must therefore reject the term "cancer chemotherapist" as too restrictive. Cancer chemotherapy implies the modality of drug administration alone, as opposed to other therapeutic procedures that are unique, such as surgery, or repeated less frequently, such as radiotherapy. And this, up to a certain extent, excludes continuous contact with the medical and psychological problems of the patient. From this viewpoint it is important to underline the differences between the medical oncologist and the other clinical oncologists, that is surgical oncologists and radiation therapists. For medical oncologists, following up their patients means maintaining contact with patients who have a chronic disease, following up their problems over some months or years. Patients with advanced cancer are generally in a low state compared with other surgical patients, with poor performance status, psychological depression and, often, persistent anxiety. A medical oncologist should also deal with medical aspects that are not directly related to cancer but rather to other organ dysfunction, which might have existed before the development of cancer, such as liver insufficiency, heart disease, renal impairment, and cardiac failure, and with the treatment of infections.

For better understanding of our role, more detail is needed in terms of definition of our speciality. There is for example also a difference between ourselves and specialists following patients with cancer pain. We are aware that our usual therapeutic approach is an agent that might itself be active in the cancer patient. This means that hope is transmitted to the patient even by nonverbal means, by our active attitude. Hope is not directly related to the percentage response rate achievable, but only to whether or not response is a possibility. While he was Prime Minister, Harold Wilson said, "To the man without a job, unemployment is 100%". This could be adapted for the only patient out of 100 patients to achieve complete or partial remission: for such a patient this remission is 100%. This is obviously not a scientific attitude, but hope is important for patients with cancer. A reasonable degree of hope means a better quality of life. From a psychological point of view this is quite useful and weighs more heavily than some of the distressing toxic side effects of anticancer chemotherapy.. We should also think that psychologically, continuous medical care is even more valuable than results (complete remission, partial remission, duration of a complete remission or of survival). This continuity in contact with the patient comes about because the administration of the treatment means we follow these patients regularly without abandoning them. Too much criticism of an active attitude in scarcely responding neoplasms comes from forgetfulness of the time in which patients were abandoned simply because it seemed the agents available could not possibly be useful. They were deceived and given no infor-

mation; pathetic lies were offered to play down their problems, but the patients saw through this.

In conclusion, we should be aware that psychologically the situation has been changing for the better for the patient, insofar as we are now able to give the patient hope simply because we believe that something in our therapeutic armamentarium may offer the possibility of relief.

We have been trying here to give a brief outline of our historical role, but there are other possibilities for the future: medical oncologists should be the natural interlocutors of basic research people. This means that in our own research activity we should be in close contact with clinical, cellular and molecular pharmacologists. Close contact should be maintained with molecular biologists, in particular, even if they speak a completely different language. We should try to reach a cultural level that will allow us to communicate with people working in this field. But a mutual effort is also needed, because when knowledge is achieved this can be more naturally transferrred through the hands of medical oncologists than of other specialists in different fields of clinical oncology.

Another area in which medical oncologists should take a new, quite active attitude in Europe is that of smoking. Smoking is estimated to cause around 30% of all cancers (lung, oesophagus, pharynx and mouth, bladder). Smoking is the prime cause of increasing lung cancer, which is the most common neoplasm in the world. Therefore, European medical oncologists should join and/or promote programmes to control smoking and set for themselves a code of ethics, which means not smoking in public. This practical attitude towards prevention of a disease which is preventable is the best response to a false dilemma based on oversimplification: it has been requested that more money should be spent on prevention than treatment [5]. More money should definitely be spent on the prevention of neoplasms in which this is a possibility, such as lung cancer, or in which an early diagnosis is possible, such as cervical carcinoma, but for other neoplasms, such as leukaemia and lymphomas, more money should be spent on research into treatment, since at present there are no real means of preventing these kinds of chemosensitive tumours or other neoplasms. The conclusion is that more money should be spent where it is worth while, and not only in one direction, but at least in two different directions.

As medical oncologists, we have the task of continuing to look for new agents. This will take time, but I believe that our activities will meet with success. Medical oncologists have been described by an outside observer [20] as needing to be peculiar types, in the sense that they have to be satisfied with little success. While being frustrated by many therapeutic failures, at the same time we have been devoting ourselves for years to clinical research. To continue along this path (often despite lack of success), according to this observer, a particular *Weltanschauung* is required. This peculiar feature will probably make it possible for us to continue our work in this direction.

The present role of the European Society for Medical Oncology

Since its early days, the European Society for Medical Oncology has been providing a forum for mutual exchange of information on the latest results of research in the field of cancer chemotherapy. Over the years, this society has been facilitating close contact among European medical oncologists. Teaching activities have been promoted by some of the members of the society through the European School of Oncology. More recently, quite constructive interaction with the other European Oncological Societies, such as the European Society for Surgical Oncology, the European Society for Radiation Oncology and other Oncological Societies in Europe, has developed, resulting in foundation of the European Federation of Oncological Societies in Europe, which organizes the European Conference on Clinical Oncology every 2 years. The objective of this oncological meeting is to provide a forum for young European medical oncologists without the necessity for crossing the Atlantic Ocean and participating in American ASCO-AACR meetings every year, which means substantial financial savings for young scientists who have not yet reached the stage of being sponsored by their institutions.

In view of this changing situation, it must be recognized that from the middle to the end of the last decade European clinical oncologists had more opportunity to meet and get to know each other in the United States than in Europe. We believe, however, that now the time has come to exchange information directly in Europe, since European oncology has reached a level at which, while some input is definitely still possible from the United States, some valuable information can also be given to scientists in the United States. In order to conserve financial resources, an oncological forum is needed in present-day Europe for the rapid exchange of research experience.

When the European Society was founded French-speaking members were predominant, then Mediterranean members as Italian and Spanish participation increased, but later on, the society also became active in Northern Europe. This means that the society's objective for the future is further growth in Northern Europe and development in Eastern Europe.

The society needs stronger organization and management. We would like to have many more meetings under the sponsorship of the European Society of Medical Oncology. Working committees should be established for specific purposes, and links with the press should be strengthened in the future.

The society might be in a position to make recommendations to medical oncologists in key positions in our field of activity. It goes without saying that it is essential to be open to cultural development in the interface activity between our discipline and basic research, but from a more practical point of view we have to make sure that medical oncology becomes definitely accepted as a formally established speciality in Europe. We need official recognition; this is already available in some countries, e.g. Spain, but not yet in mast other countries in the European Community. We must push for new cancer treatment establishments, which means oncological institutes, divisions and services. All of our actions must be characterized by a European approach to the problem, which means moving within the framework of the EORTC, of the European Organization of Cancer Institutes and of the Federation of the European Oncological Societies; the European Community may have a part to play in progress in the field of clinical and experimental oncology.

The scientific task is the major part of our society's work, but it is only one part of it. Any one of us should be ready to interact with the press and political authorities on

progress made in cancer research and treatment. Future activities undertaken in Europe by our society will then provide the impulse for research in the field of medical oncology, requests for the initiation of new specific cancer treatment establishments, recognition of the specialty in Europe, and requests for an increase in the cancer research budget in the European Community.

Conclusions

For some medical oncologists all this might have seemed unduly pessimistic, but rumours have recently been started in the press and by other scientists about the toxicity of cancer chemotherapy [13] and the real advantages of cancer treatment. Problems of cost benefit have been discussed, and the conclusion put forward that costs far exceed benefits in the medical treatment of cancer patients. We should be able to counter with the facts and not with mere opinion. The position of the Food and Drug Administration may be a simple reflection of public and political opinion of the expenditure that should be available for cancer research. We must be aware of this problem with regard to the future of medical oncology. This somewhat pessimistic outlook, however, is coexistent with optimistic expectations about future possibilities in the field of medical cancer treatment. Nonetheless, we have to be patient, because future developments may well take a good many years.

The practice of medical oncology can be compared in some ways to the efforts of Sisiphus; even a complete remission can be followed by a relapse. The stone is rolled up the mountain (complete remission), and then it rolls down again (relapse). But just as Sisiphus never stopped in his efforts to take the stones up the mountain, I think we will try again and again, with the same patients and/or with others. This is part of our task and we shall continue with this probably endless job.

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