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Improving Cancer Survival in the Next Century

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The number of cancer cases continues to increase worldwide, but progress is being made in reducing the incidence of specific types of cancer. As our understanding of the pathological mechanisms involved in tumorigenesis has increased, so has the availability of newer and more potent chemotherapeutic agents. New drugs such as the taxoids and camptothecins, new uses for old drugs such as thalidomide and minocycline, and the advent of biological response modifiers such as the interferons, interleukins and tumour necrosis factor, have enabled researchers to develop more sophisticated, multistep protocols for cancer management, particularly in cases where the results of standard treatments have been disappointing. Research towards the development of vaccines against some cancers, such as melanoma and cervical cancer, is underway. Investigation of the feasibility of using gene therapy to influence or suppress the growth of neoplasms is another area of research. Another approach to improving patient survival involves assessing the treatment centre location and the personnel on the cancer management team. A number of recent studies have demonstrated that diagnosis and care by specialists in team-centred units results in significantly less morbidity and significantly greater long-term survival in many types of cancer. Cancer management will soon benefit from the many newly available screening techniques for predicting susceptibility to various types of tumours, decreasing environmental exposure to known carcinogens (especially tobacco products), and rapid diagnosis of cancer in the earliest stages. Once the cancer has been diagnosed, precise staging of the tumour to maximise the efficacy of multidrug and adjuvant treatment regimens will be necessary, along with improved surgical techniques to increase the chances of curative resection and improved radiological techniques to minimise exposure of normal tissue. Aggressive methods to locate and destroy residual tumour and/or distant metastases will be routinely employed to optimise further long-term survival. Rapid dissemination of information regarding new treatments and rigorous adherence to quality control and to protocols that have demonstrated their effectiveness should improve a patient's chances of surviving a cancer diagnosis in the next century. © **1997 Published by Elsevier Science Ltd.**

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INTRODUCTION

THE NUMBER of cancer cases continues to increase worldwide, with over 10 million cases per year predicted by the year 2000. Cure, which can be defined as symptom-free survival at 5 years post-treatment, is expected in approximately 45% of cases. Sixty-five percent of patients diagnosed with cancer will die with metastatic disease; 35% will die as a result of local treatment failure [1]. Although progress is being made in reducing the incidence of specific types of cancer, clearly, new treatment strategies are urgently needed.

Endeavours to improve the survival rates for patients with solid tumours have taken a number of different directions in recent years. Certainly, the availability of newer and more potent chemotherapeutic agents is an encouraging development, however, this is not the only avenue being pursued. As our understanding of the pathological mechanisms involved in tumorigenesis has increased, so have the potential means of interfering with these processes.

In the future, physicians may be able to use vaccines to inhibit the development of tumours that are virally induced and to treat other tumours, such as melanomas which selectively express different antigens [2, 3]. Another approach is to deny the cancerous tissue nutritional support by inhibiting tumour-induced angiogenesis [4]. Immunotherapy (e.g. monoclonal antibody preparations) involves the design of antigen-directed therapeutic agents that would provide more accurate targeting of specific cancers. The use of biological response modifiers (BRMs), such as interferons, interleukins

and tumour necrosis factor (TNF) could augment the host's natural defenses against the growth of tumour cells. As progress in gene therapy continues, we may one day find that introduction of extraneous altered genetic material can be used to turn the cancer cell's metabolic processes against itself, producing substances that induce the cell's destruction. Alternatively, administration of substances such as antisense oligonucleotides can inhibit carcinogenic processes within the cell itself by interfering with the synthesis of vital proteins.

Another approach to improving patient survival involves the fundamental issues of who administers treatment (i.e. specialist or generalist) and how those treatments are administered (i.e. in what type of clinical environment). These types of data are only now beginning to be collected, analysed and published in trials large enough to provide more than anecdotal evidence of the influence that treatment setting and practitioner competence can exert on the outcome of cancer therapy. With the increasing trend toward some type of managed-care medical environment, the ability to direct patients to centres with proven records of success in the treatment of specific cancers has the potential to significantly affect patient survival rates over time.

This review will examine the various factors that contribute to successful treatment outcomes with cancer and will briefly summarise the new directions in the treatment of solid tumours.

FACTORS INFLUENCING TREATMENT OUTCOME

Type, size and distribution of tumour

Treatment outcome will depend upon the type, size and distribution (clinically detectable and undetectable metastases) of the tumour. Obviously, some types of tumours are inherently less curable than others, due either to aggressive growth or metastatic behaviour (e.g. malignant melanoma, ovarian cancer) or a paucity of effective treatment options (e.g. malignant melanoma, renal cell carcinoma, non-small cell lung cancer). When the response rate and survival with standard treatment is low, participation in clinical trials with experimental therapies may provide some hope for increased survival.

Tumour size influences the likelihood of success for many treatment modalities, as penetration of systemically administered drugs to the interior of a solid mass may be poor. Normally, in the case of local disease, the optimal treatment is either surgery and/or radiotherapy. However, when curative resection is not possible, debulking of large tumour masses usually precedes chemotherapy. In addition, the spread of metastases to areas such as the brain, which is shielded from many pharmacological agents by the blood–brain barrier, or to tissues that are comparatively poorly perfused (e.g. bone) will limit the effectiveness of systemic chemotherapy [5].

Tumour staging

After histological proof of cancer has been obtained, staging procedures specific to different tumour types should be performed. The level of experience of the pathologist, as well as the information he/she provides about pathological features, can be a prime determinant of staging accuracy, as can information from the surgeon after resection or debulking. In many cases, both the choice of therapy and its ultimate success are functions of tumour stage. Thereafter, optimal treatment should be determined by employing the multi-modality approach, which is now practiced in oncology centres.

Hospital and surgeon

Recently published literature provided objective evidence that treatment outcome is influenced by the treating physician or surgeon and location of treatment (i.e. teaching versus non-teaching hospital).

In 1991, Gillis and associates [6] noted that resections described as 'curative' for ovarian cancer occurred more often in teaching hospitals than in non-teaching hospitals (71% versus 51%). These data were compiled from all ovarian cancer cases treated in the west of Scotland in 1974. Long-term survival (at 5 and 10 years) showed a clear benefit when patients were treated in teaching hospitals. These differences could not be accounted for by differences in patient age, histology, clinical practice or year of treatment. A subsequent article retrospectively examining the management of 479 ovarian cancer cases diagnosed in the same geographic area in 1987 demonstrated similar results [7]. Improved survival was demonstrated for those patients who underwent specialist care in a multidisciplinary team setting. Specifically, patients who were seen initially by a gynaecologist had a 5-year survival rate of 35% compared with 16% for patients seen first by other types of physicians. When surgery was performed by a gynaecologist, the 5-year survival rate was 28% compared with 14% in patients who had operations by a general surgeon. Lastly, patients who attended a multidisciplinary clinic were more than twice as likely to receive a treatment regimen that included platinum, which also was associated with improved postsurgical survival.

Subsequent publications revealed similar patterns of improved outcomes following specialist or specialist unit care for patients with breast cancer [8, 9], colorectal cancer [10, 11], and non-seminomatous germ-cell tumours [12]

Sainsbury and associates evaluated 12 861 patients with breast cancer treated between 1979 and 1988 in Yorkshire, U.K. [8]. Considerable variation in the use of chemotherapy and hormone therapy was observed among physicians (0–46%). The patients of those physicians who used these types of treatments had greater survival rates. The estimated gain in 5-year survival, had all physicians utilised the treatment protocols used by the most successful practitioners, was estimated at 4–5%. In addition, an effect of caseload also was observed, with physicians treating more than 30 cases per year achieving better results than those treating less than 30 cases per year. The authors concluded that this effect was not solely due to the number of patients treated but also was a measure of the organisation of the treatment team and its ability to bring together all of the clinical skills necessary for optimum treatment. An even greater benefit for 5- and 10-year survival (9% and 8%, respectively) was found by Gillis and Hole in a retrospective 1996 study of 3786 breast cancer patients in the U.K. [9]. Improved survival was observed for all age groups, for those with small and large tumours, and for each socio-economic stratum evaluated. Thus, the authors stated that the true benefit of specialist care was attributed to the better level of care provided (surgery plus additional therapy and medical resources), rather than the type of patient evaluated by the specialists.

Differences in treatment outcomes as a function of the surgeon and the treating institution were also investigated for patients with colorectal cancer. McArdle and Hole [11] assessed postoperative complications, mortality and survival in a group of 645 patients cared for by 13 surgeons in the U.K., none of whom were specialists in colorectal cancer.

The proportion of patients undergoing curative resection ranged from 40 to 76%, and overall postoperative mortality varied from 8 to 30% among surgeons. Ten-year survival for patients undergoing curative resection ranged from 20 to 63%. The incidence of wound sepsis, wound dehiscence, chest infection, anastomotic leakage and pelvic or subphrenic abscesses also varied considerably by surgeon. In a German study of prognostic factors for 1121 patients with invasive rectal carcinoma, it was found that both the treating institution and the individual surgeon were independent variables affecting the frequency of tumour recurrence and patient survival [10]. Locoregional recurrence varied from 4 to 55% for individual surgeons, with the surgeons performing a low frequency of operations experiencing the highest number of recurrences and an overall lower survival rate. This could be explained by the differences in the quality of surgery, as well as by tumour-related prognostic factors.

Harding and colleagues [12] examined the impact of referral to a group of five specialist tertiary referral centres in the U.K. for a group of 440 men with non-seminomatous germ-cell tumours. This study demonstrated that the treatment unit administering therapy was an independent prognostic factor for survival. The most successful facility treated more patients overall ($n = 235$) and more patients with an unfavourable prognosis than did the other four clinical centers combined ($n = 194$). Despite these factors, the relative death rate was 2.65 times higher at the other four units combined compared with the most successful facility. The authors suggested that the main benefit provided by such successful clinical centres is strict adherence to proven treatment protocols, in addition to access to multidisciplinary clinical expertise in oncology, radiology, pathology, biochemistry and surgery, an observation that is in accordance with many of the studies mentioned above.

Published studies to date have dealt primarily with patients undergoing surgery and chemotherapy. However, radiotherapeutic procedures may also benefit from protocol standardisation and strict quality control measures. Although no published data exist on the patient cost (in increased morbidity and mortality) of errors during radiotherapy, anecdotal evidence suggests that the same possibilities for wide variation probably exist here as well. Clearly, the body area exposed and the radiation dose and schedule will have profound effects on treatment efficacy and long-term outcome. Both random, accidental errors and systematic, repetitive errors can occur among institutions and departments. For instance, large variances in beam calibration (i.e. 5–10% or more) can result in exposure of more normal tissue to ionising radiation, with the predictable adverse consequences for the patient. Mandatory quality control programmes could alleviate many of these problems.

In an editorial by Gallagher [13], the importance of quality assurance for multi-institutional and international clinical trials was stressed. The Radiation Therapy Oncology Group (RTOG) is a multi-institutional organisation funded by the National Cancer Institute (NCI) that requires its members to provide information regarding their radiation equipment, staffing, enrollment of patients into protocols and Institutional Review Board approval. Minimum standards for participation in the group are put forth by a membership committee, and all members are subjected to ongoing quality control. Because it is a constant challenge to maintain quality control for the European Organization for Research and Treatment of Cancer (EORTC) clinical research sites, the Cooperative Group of Radiotherapy of the EORTC decided to initiate a quality assurance programme over 10 years ago to evaluate the equipment and personnel of 50 centres that were participating in clinical research protocols in radiotherapy [14]. They compared data collected in the early 1980s to the present time, often finding imbalances in equipment usage and staff time among institutions. They concluded that their database would be updated frequently, and offer guidelines for minimum recommendations for European radiotherapy departments involved in clinical research.

As a result of the aforementioned studies, and other, similar studies, the evidence in favour of specialist and multidisciplinary 'team-approach' care has become so compelling that a 1995 editorial in the *Lancet* suggested a re-evaluation of the manner in which patients are referred for cancer treatment in the U.K. [15]. Referral to an appropriate treatment facility is especially important in cases where the type of cancer is so rare that specialised treatment is needed. If treatment requires highly specialised skills or knowledge, or if expensive equipment and/or large medical teams are needed to handle each case, specialist units would also provide an advantage. Lastly, such centres would be more likely to have knowledge of, and access to, the latest experimental therapies and protocols for the treatment of tumours that are unresponsive to standard regimens. It has been demonstrated repeatedly in studies that patients treated in a clinical trial fare much better than those treated with standard therapy. This is most likely because the medical team adheres to strict study guidelines, subsequently improving patient outcomes.

NEW TREATMENT MODALITIES

It is gratifying that so many new drugs and new treatment strategies for solid tumours are being introduced, since many of these tumours are very difficult to treat adequately with standard regimens. A renewed appreciation for the potential of agents derived from natural products has led to several promising new drugs. New therapies also are being developed as a consequence of an increasingly sophisticated understanding of the molecular and cellular processes involved in carcinogenesis and the natural defenses that the body is capable of mounting in response to such events. Each step in the cellular or physiological cascade of events may be viewed as a potential point of intervention for therapeutic purposes. Investigators in the fields of immunotherapy, gene therapy, and the use of BRMs have made particularly good use of this type of basic information in developing their research strategies.

Drugs

Paclitaxel (Taxol), originally derived from the bark of the Pacific yew tree, has proven to be a valuable addition to the therapeutic armamentarium for breast and ovarian cancers and non-small cell lung cancer [16]. In addition, the agent has shown some promise in the treatment of small-cell lung cancer and head and neck cancers. Further studies are underway to examine the use of paclitaxel in multidrug regimens. Docetaxel (Taxotere), a semisynthetic taxoid is also available for the treatment of anthracycline-resistant breast cancer and has shown promise in non-small cell lung cancer; it is also being investigated in combination with other agents in a number of different tumours. These taxoids exert antitumour effects by binding to tubulin and inhibiting cell

division. Camptothecins (e.g. topotecan, CPT-11) are derived from a tree native to the southern regions of China and are being evaluated for use against ovarian, colorectal and non-small cell lung cancers. These compounds inhibit the nuclear enzyme topoisomerase I, which is involved in deoxyribonucleic acid (DNA) replication [17, 18]. Protein kinase-C inhibitors, such as briostatin, are another class of new compounds being developed for the treatment of cancers.

In addition to drugs derived from natural sources, advances in the development of other types of drugs have been occurring as well. Antimetabolites (e.g. methotrexate, mercaptopurine, 5-fluorouracil) have been used for nearly 40 years [5]. These drugs mimic endogenous molecules and bind selectively to cellular constituents, thereby inhibiting the production of compounds that are vital to cell function (enzymes, cofactors, genetic material), resulting in cellular dysfunction and/or the eventual death of the cell. New antimetabolites such as tomudex, capecitabine and gemcitabine have been developed that may offer advantages in potency, selectivity and tolerability over earlier drugs. Older, non-neoplastic agents such as minocycline and thalidomide have been shown, in animal models, to inhibit tumour angiogenesis and disrupt collagen synthesis and deposition, denying the nutrients supplied by vascular perfusion of the solid tumour mass [19, 20]. Other new groups of drugs are the signal transduction inhibitors and matrix metalloproteinase inhibitors. While these drugs have just started to be investigated in clinical trials, the first results look promising [21].

Antisense oligonucleotides are yet another new approach to cancer therapy [22]. This class of compounds binds to and disables messenger ribonucleic acid (mRNA), thus inhibiting the synthesis of specific cellular proteins. If the protein is expressed only by neoplastic cells, such antisense-type inhibition might be able to selectively eliminate those cells. Research on antisense oligonucleotide therapy in cancer treatment is still in the early stages.

Biological response modifiers (BRMs)

As knowledge about the enormous complexity of the cellular processes that result in an immune response to an invading tumour increases, many potential opportunities to modulate this response have also become apparent. Initial enthusiasm for the treatment possibilities with the BRMs has been tempered by the limited clinical response associated with these agents and their toxicity, particularly when used as single agents [23, 24]. Nonetheless, interest in the role of these substances continues, and their use in multiagent treatment regimens is being investigated. Various BRMs are discussed below.

Interferons (IFN-α, -β, and -γ) have found a niche in the treatment of some cancers that have proven resistant to other chemotherapeutic regimens. IFN-α is the most widely studied of these compounds and has shown activity against malignant melanoma and renal cell carcinoma. When IFN-α is used in combination with conventional chemotherapeutic agents, efficacy has been promising in the treatment of ovarian, breast, bladder, cervical and colorectal cancers, as well as non-small cell lung cancer [24]. Local (intralesional) administration of IFN-α also has been investigated for certain types of cancers.

Cytokines, including the interleukins (IL-2, -4 and -6) and TNF have been employed as single-agent therapy and in combination with conventional regimens [23], but have elicited few clinical responses. In addition, many of these compounds exhibit considerable toxicity, such as fever, chills, nausea and vomiting, hypotension, and capillary leak syndrome. It is hoped that the use of these agents in combination with each other or with standard therapies can decrease the incidence of severe side-effects while maintaining antitumour efficacy. Interleukin-2 has been approved for treatment of renal cell carcinoma, where it has been shown to be effective in 15–30% of patients. Immune function stimulation by IL-2 results in lymphoid cell proliferation, induction of cytotoxicity in other lymphoid cells, and stimulates production of other cytokines such as other interleukins, TNF and IFN-γ.

Vaccines

In the future, it may be possible to vaccinate against certain viruses known to be causative for some types of tumours. It is known that 18% of all tumours develop with viruses as a cofactor. For instance, human papillomavirus 16 (HPV 16) is associated with cervical cancer, and hepatitis C with hepatocellular carcinoma [25]. It may be assumed that vaccination against these viral agents might prevent the development of the malignancy. Antigens encoded by genes that are selectively expressed in tumours (such as melanomas, head and neck tumours, non-small cell lung cancers, and bladder carcinomas) have been identified [2]. In addition to this, the development of antitumour immunisation strategies has been aided by a better understanding of the role of costimulatory molecules and cytokines in immune regulation and T-cell activation [2].

Immunotherapy

Rietmüller and colleagues [26] reported the results of a multicentre randomised clinical trial of murine monoclonal antibodies in 189 patients with Dukes' class C colorectal carcinoma. These antibodies recognise a cell surface glycoprotein (17-1A antigen) expressed by both normal and malignant epithelial cells, and stimulate an immune response to the remaining cancer cells. The antibody preparation can be useful in targeting minimal residual disease present after curative tumour resection. Mortality in patients receiving the monoclonal antibody preparation was reduced by 30% compared with patients who were only under observation following resection. Patients who experienced distant metastases as the first sign of relapse responded better to monoclonal antibody than did patients with local recurrence. After 5 years, the recurrence rate in patients who received the antibody preparation was reduced by 27% compared with patients under observation only. These results were comparable to those observed with more conventional therapies, such as fluorouracil and levamisole or fluorouracil with semustine plus postoperative radiotherapy. Although one drawback of monoclonal antibody treatment is the high likelihood of development of an immune response to the preparation after multiple uses, the occurrence of an immune response was not associated with major side-effects in this study. The authors concluded that immunotherapy may ultimately be most useful as adjuvant therapy after standard chemotherapeutic regimens.

Gene therapy

One of the newest methods of attacking cancer cells is gene therapy, altering the genetic instructions of a specific tumour cell so that a desired gene product is expressed when these

cells are re-introduced into the patient. Thus, tumour cells derived from the patient could be forced to synthesise various BRMs that would facilitate the identification of the tumour by the host's immune system [3, 27]. The body's natural defenses could be brought into play to destroy residual tumour cells after primary treatment. Genetic material also can be introduced into the body by insertion into otherwise harmless viruses. The virus acts as a vector, transferring the foreign DNA sequence into the host cell resulting in the expression of the desired molecule by the cell. Retroviruses have been used for this procedure [3, 28], although some safety concerns about the unknown effects of introduction of such viruses persist. Recombinant adenoviruses also are being investigated for this purpose, because they have not been associated with any diseases and can integrate themselves at specific sites on the human genome; this technique has been tested in a phase I study in lung cancer [29]. Alternative, non-viral methods include the use of liposomes containing the genetic material or insertion by means of a 'gene gun' that launches plasmid-coated microprojectiles into the cell [27]. The first reports of such genetic manipulation have shown promising results [28, 29], but the data are preliminary and the sample sizes must be increased in order to make valid conclusions.

FUTURE DIRECTIONS IN CANCER TREATMENT

In the future, cancer management may begin long before a diagnosis is made in an individual. Family history has long been used to estimate the likelihood that a particular individual may, at some future time, develop a malignancy. Recent advances also have made it possible to examine genetic material to detect the presence of specific genes that are known to predispose the carrier to some cancers (e.g. breast and colon cancers). Presently, these procedures are very expensive, time consuming, and are not suitable for widespread screening. The use of vaccines to prevent virally induced cancers may also become widespread in the near future.

Much information has been gained about environmentally caused cancers in the past decades, and major steps have been taken to reduce or eliminate the exposure of the population to known carcinogens. In some countries, these efforts have yielded good results, and the overall incidence of such cancers there has been declining in recent years. One instance in which the opposite has been true is the constellation of cancers associated with the use of tobacco products, including cancers of the lung, mouth, oesophagus, larynx, pharynx, bladder and pancreas. While the death rate from lung cancer has been steadily decreasing in non-smokers, rates have increased in those who continue to smoke [30]. Death and disease from tobacco products is a worldwide scourge—one that is hitting the third-world nations particularly hard. Although the percentage of persons in some developed countries who continue to smoke has been significantly reduced over the years, that percentage in the third world has rapidly increased. A corresponding epidemic of tobacco-related illnesses in these countries has predictably developed and can only worsen over the next few decades, unless aggressive measures are taken.

Once a cancer has been diagnosed, precise staging of the tumour will be performed in order to evaluate the potential for metastasis and to maximise the efficacy of any proposed multidrug and adjuvant treatment regimens. Such treatments may include chemotherapeutic agents along with hormones or BRMs. It may also be possible to use pharmacokinetic analysis to predict the clinical response of tumour cells to a drug in advance of administering that drug to the patient, as shown in a recent paper using 5-fluorouracil in solid tumours [31]. Improved surgical techniques will increase the chances of curative resection, while improved radiological techniques will maximise tumour destruction and minimise the exposure of normal tissue. After the initial treatment intervention (surgery, radiotherapy, chemotherapy), aggressive methods will be used to find and destroy any residual tumour and/or distant metastases, in order to further optimise the patient's long-term prospects for survival. Techniques such as immunotherapy or gene therapy could prove highly useful in this respect.

There is a need for high quality multinational clinical research to improve cancer care and decrease mortality. To achieve this, the EORTC was established to merge the facilities and expertise of many multinational and multidisciplinary groups to provide the highest quality of cancer treatment. The goal of the EORTC is to develop, conduct and stimulate clinical research in cancer treatment through the coordinated efforts of many institutions. It is divided into four major divisions of Treatment, Research, Education and Training, and Prevention Research, as well as six specialty units (with the addition of new units as the need arises). The presence of the EORTC promises excellent cancer clinical research as well as the dissemination of information to encourage other physicians, who might not have access to a research centre and the latest information regarding new treatments, to enroll their patients in state-of-the-art clinical protocols. By adhering to rigid quality control, by conducting high quality protocols, and by rapidly disseminating information to all physicians who treat cancer patients, the EORTC hopes to dramatically improve a patient's chances of surviving a cancer diagnosis in the next century.

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