Chemotherapy of solid tumours

Report of a
WHO Expert Committee

hnical Report Series

World Health Organization, Geneva 1977

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WHO EXPERT COMMITTEE ON CHEMOTHERAPY OF SOLID TUMOURS

Geneva, 1–5 November 1976

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CHEMOTHERAPY OF SOLID TUMOURS

Report of a WHO Expert Committee

A WHO Expert Committee on Chemotherapy of Solid Tumours met in Geneva from 1 to 5 November 1976. Dr M. A. Akhmeteli, Director, Division of Noncommunicable Diseases, opened the meeting on behalf of the Director-General. He emphasized the growing importance of chemotherapy in cancer management and the need for information on chemotherapy to be readily available to doctors working in all countries. The subject was of particular significance for developing countries because chemotherapy was used primarily in the advanced stages of cancer and required less technical equipment and manpower than did surgery and radiotherapy.

INTRODUCTION

The ultimate goal of the treatment of cancer is cure. It is therefore essential that patients for whom this goal represents a reasonable possibility be identified. This can be done only through a definitive evaluation of the pathology and a precise assessment (staging) of the extent of the disease. The latter may require, in addition to the classical clinical evaluation (e.g., TNM staging), the integrated application of diagnostic radiology, nuclear medicine (particularly scanning), and endoscopic, laboratory and occasionally surgical staging techniques. If the patient proves to be a candidate for curative treatment it must be recognized, firstly, that the opportunity for curative treatment depends on the application of optimal therapy from the outset (if the initial treatment fails the opportunity for curative treatment is markedly reduced) and, secondly, that the curative treatment increasingly requires an integrated approach using a variety of treatment modalities. Increasingly this involves the use of surgery and/or radiotherapy to control local or regional disease combined with chemotherapy. In the not-too-distant future immunotherapy may also be used for the control of micrometastatic disease in high-risk patients.

For patients in whom treatment with curative intent is unrealistic, palliative approaches usually involving the sequential application of therapeutic modalities (including hormonal therapy) may substantially improve the quality of life.

Cancer medicine involves much of general medicine, and cancer treatment may produce both acute and delayed side-effects. It is therefore essential that such treatment be conducted in a setting where these general and oncological medical problems and complications can be effectively managed. In view of this and the need to perform definitive staging and initial treatment at the same place, a careful assessment of whether the patient should be treated locally or referred to a special centre should be made immediately following diagnosis.

1. TREATMENT MODALITIES

Chemotherapy is one of the major modalities available for the treatment of cancer. Since the discovery of the antitumour action of nitrogen mustard during the mid-1940s, chemotherapy has developed rapidly to a stage in which it is involved in a wide range of palliative and some curative therapies and constitutes a separate discipline. Its continuing and growing success will ultimately increase greatly not only the numbers of cured cancer patients but also those in whom the disease has been converted from an acutely dangerous life-threatening condition to a chronic disease. It is necessary to be aware of the socioeconomic problems that such changes may entail.

1.1 Types of treatment

The basic assumption in cancer treatment is that all malignant cells should be destroyed, removed, or neutralized to achieve cure. In practice, five kinds of treatment may do this—surgery, radiotherapy, chemotherapy, endocrinotherapy and possibly immunotherapy. Some modalities are more successful than others but all are incompletely understood and all need more study.

For some tumours a specific therapeutic procedure may represent the only choice of treatment while for others a number of satisfactory alternatives may exist. In the latter case, optimal therapy is determined not only by the nature and extent of the disease but also by the experience of the attending physician and the facilities available for treatment.

Surgery is the most frequently used method of treatment. The proper application of surgical techniques is responsible, for example, for achieving 5-year survival (although not necessarily achieving cure) in about 50% of women with breast cancer and in approximately 30–40% of patients with cancer of the colon.

Radiotherapy is also important as a means of controlling a wide variety of local or regional solid tumours. It is used either in combination with surgery or alone. Radiotherapy is successful in curing local disease in at least 90% of men with seminoma of the testis, at least 80% of children with retinoblastoma, and about 50% of patients with local squamous cell carcinoma of the nasopharynx.

Chemotherapy is a relatively new science compared to surgery and radiotherapy, but it has already been successful in reducing the mortality in a number of different diseases. Drugs alone can cure significant numbers of patients with some forms of cancer such as gestational choriocarcinoma and Burkitt's lymphoma. There are other cancers (acute lymphoid leukaemia, Hodgkin's disease, histiocytic lymphomas, Ewing's tumour, Wilms' tumour, embryonal rhabdomyosarcoma, testicular tumours and retinoblastoma) in which chemotherapy, either alone or in combination with other kinds of treatment, can bring about normal life expectancy in a significant percentage of patients with advanced disease. The proportion of patients achieving normal life expectancy ranges from about 80% of those with Wilms' tumour to about 15% of those with metastatic testicular tumour.

Endocrine treatment involves the manipulation of hormonal concentrations in the patient and is designed to influence the behaviour of tumours growing in hormone-dependent organs such as the breast and prostate. Particularly important is the concept that endocrinotherapy is relatively non-toxic to normal tissues. For the purpose of this report endocrinotherapy will be considered as part of cancer chemotherapy.

In theory, immunotherapy could be useful in treating both localized and disseminated disease, but in terms of practical results it is still in its early phase of development.

1.2 Factors limiting curative potential of applied therapy

Cancer can be classified into two major categories : solid tumours and haematological malignancies. Solid tumours are initially confined to specific tissue or organ sites. In time, however, cancer cells break off from the original tumour mass, enter the blood or lymph system, reach distant parts of the body, and start secondary growth there (metastasis). When this occurs, the disease is in the disseminated stage. Conversely, haematological malignancies involve the blood and lymph systems, and for this reason, they are frequently disseminated at the time of initial presentation.

For solid tumours, surgery and/or radiotherapy are the traditional initial treatments. Neither modality is curative once the disease has metastasized beyond the local region (primary site and nearby lymph nodes) or has involved a vital organ extensively. Chemotherapy has been relegated almost exclusively to secondary or tertiary treatment of solid tumours—i.e., it is used when surgery and radiotherapy fail.

Since the highest curative potential for solid tumours exists when the tumour is both small and localized, early detection offers the best opportunity for control. However, at the time of initial diagnosis, a number of patients already have extensive disease which local treatment modalities cannot cure. Alternatively, by the time of primary therapy, some other patients have established microscopic foci of metastatic disease which available diagnostic techniques cannot detect and local treatment modalities cannot remove or destroy. In this case, it erroneously appears that the tumour is still localized. Relapses after surgery and/or radiotherapy are largely attributable to metastatic spread prior to treatment. This is not to deny, however, that in certain situations development of additional primary tumour growths at other anatomical sites could be responsible for the reappearance of the disease.

Extensive local involvement of a vital organ and metastatic spread are factors limiting the curative potential of surgery and radiotherapy, so that eradication of the last neoplastic cell requires systemic treatment. Systemic modalities used for secondary or tertiary treatment, however, are rarely successful in curing any tumours, including haematological malignancies. It is understandable, therefore, that chemotherapy as now used in patients with solid tumours is often not curative, despite the fact that some tumour regression, some subjective benefit and some increases in survival are being achieved.

1.3 Requirements for improving cancer therapy

Simply stated, the long-term goal of cancer treatment is to achieve normal life expectancy in cancer patients. On a shorter time-scale, the goals are to increase the number of patients responding to treatment, to prolong the period of remission, and to improve the quality of life. To achieve these goals, new experimental treatment strategies should be designed, based not only on research and development to improve the curative potential of individual treatment modalities but also on detailed understanding of relevant factors in cancer biology, in host biology, and in individual tumour behaviour. Moreover clinical results must be

continually collected and analysed to determine whether or not each new strategy is superior to the best conventional therapy.

Cancer is often thought of as a single disease whereas, in fact, it is about a hundred different diseases. All cancers share some common characteristics. These include : (1) unrestricted growth, (2) invasiveness of cancer cells into normal tissues or organs, (3) tendency for the diseases to spread to other parts of the body, and (4) less differentiated cell morphology. Despite such similarities, however, there are also marked differences among various forms of the disease. These differences reflect the tendency of cancer cells to retain certain characteristics of the tissue or organ of their origin.

A careful description of cancer should therefore cover many additional factors including anatomical site, histological type, and extent of disease (stage). This additional information is necessary for assessing the proper treatment and prognosis of individual patients. Clinical experience suggests that different types and stages of disease have different therapeutic requirements necessitating individual treatment strategies. Consequently an important requirement of future treatment approaches is that they must be disease-oriented rather than modality-oriented.

This report will detail the current status of the chemotherapy of solid tumours giving information on the available drugs and role of drugs in the treatment of specific kinds of malignancy. Recent investigative approaches that are highly promising will also be described. Excluded from this report will be consideration of the leukaemias and lymphomas.

2. BASIC CONCEPTS IN CANCER THERAPY

2.1 Introduction

All living things have an inherent capacity to multiply and they cease multiplication for a variety of reasons. In complex cellular organisms, such as man, a cellular " brake " is required to prevent overgrowth for the benefit of the community of cells. This appears to be controlled by an unknown feedback mechanism, probably resulting from contact phenomena when cells are crowded together. In cancerous growth, cells no longer cease multiplying when they reach a critical mass and the uncontrolled growth leads to the death of the host. In the early phases of growth, tumour cells grow exponentially but, as tumour mass increases, the time it takes a tumour to double its volume increases with it (Fig. 1). Four mechanisms have been postulated to explain