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Special article

Essential drugs for cancer therapy: A World Health Organization consultation

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Summary

The WHO has previously produced recommendations on the essential drugs required for cancer therapy. Over the last five years several new anti cancer drugs have been aggressively marketed. Most of these are costly and produce only limited benefits. We have divided currently available anti-cancer drugs into three priority groups. Curable cancers and those cancers where the cost-benefit ratio clearly favours drug treatment can be managed appropriately with regimens based on only 17 drugs. All of these are available, at relatively low cost, as generic preparations. The wide availability of these drugs should be the first priority. The second group of drugs may have some advantages in certain clinical situations. Based on current evidence, drugs in the third group are judged as currently not essential for the effective delivery of cancer care. Adequate supportive care programmes with the widespread availability of effective drugs for pain control are of considerably greater importance. The adoption of these priorities will help to optimise the effectiveness and efficiency of chemotherapy and ensure equitable access to essential drugs especially in low resource environments. Clearly this paper represents the views of its contributors. The WHO welcomes feedback from all oncologists so that the advice it gives to governments in prioritising the procurement of anti cancer drugs can be as comprehensive as possible.

Key words: chemotherapy, drugs, generics, prioritization

Introduction

Cancer is an important and increasing cause of morbidity and mortality worldwide. Currently, 10 million new cancer patients are detected each year and six million people die of the disease. We estimate that these figures will be 20 million and 10 million respectively by the year 2020. Many cancer patients, if diagnosed at an early stage and given appropriate treatment, will subsequently live a normal life-span. Useful palliation can be achieved for all patients. Effective cancer care requires the linkage of early diagnosis to the appropriate use of surgery, radiotherapy, cytotoxic and endocrine therapies as well as supportive care including analgesics, antibiotics, and blood products. Such treatments may be complex involving different specialists and not all may be available in every hospital. They are also costly making the optimal organisation of cancer services important in all economic environments.

The provision of cancer treatment services, including chemotherapy, is an essential component of a national cancer programme (NCP). These programmes offer a rational mechanism for implementing existing knowledge on primary prevention, early diagnosis, screening, optimal treatment services and symptom control. The WHO has produced a cancer priority ladder which can be adapted to the resources available and the epidemiology of cancer in a specific country. The formation of an NCP is an important health priority [1, 2]. Even with limited resources, a systematic, planned approach can yield substantial medical and social benefits. Some common tumours can be treated with a good chance of cure, so that treatment services should be readily accessible. Some relatively rare but curable cancers require highly specialised facilities for optimal care such as the acute leukaemias and paediatric tumours [3]. Unless adequate resources and facilities are available, it is inappropriate to acquire the drugs which are required to treat these cancers. For other tumours such as hepatoma and lung cancer the development of effective prevention programmes through hepatitis B immunisation and tobacco control will clearly be of greater priority than therapy for the immediate future. Downstaging strategies in breast and cervical cancer by early detection programmes and effective referral guidelines will provide a larger health gain in certain situations. The cost effectiveness of chemotherapy will clearly vary across the globally diverse epidemiological and economic spectrum.

Cancer chemotherapy, like surgery and radiation therapy is an essential component of modern cancer care. Medical staff must have appropriate training, knowledge and access to the requisite facilities to deliver and monitor chemotherapy. A properly directed and integrated team approach with experts in at least pathology, surgery, radiation therapy and medicine is essential for optimal outcomes at an acceptable cost.

To assist the WHO Expert Committee on the Use of Essential Drugs in their selection of drugs for cancer chemotherapy, the WHO invited medical oncologists from five continents to review the essential drugs list for cancer which had been formulated initially in 1985 [4] and revised in 1994 [5].

General principles

Prior to the initiation of any cancer treatment, the goal of therapy must be realistically defined. Individual prognostic factors should be determined such as the stage of disease [6], the sites of metastases, the histology of the tumour, the general medical status of the patient, the patient's willingness to accept the anticipated toxicity, and the availability of necessary facilities and personnel to treat complications. Although a particular tumour type may be curable in some instances, clearly not all patients with that tumour type will be cured. The risk – benefit concept needs to be discussed with the patient in advance. Increasingly patients are being given far more information about cancer and the options available to them. Furthermore the Internet provides a readily accessible international resource on cancer including drugs and is used by many patients and their families [7]. Commonly used sites include Oncoweb, Oncolink, Cancernet, PDQ. These are well contructed sites with reliable information. Unfortunately, the quality of many other sites is highly variable. Cancer chemotherapy requires access to laboratory facilities to monitor blood counts as well as liver and renal function. The assessment of tumour response in patients with measurable tumours must be made at appropriate intervals to determine if the treatment is effective and if the patient should continue therapy.

Some principles of chemotherapy are well established. The initial therapies employed are often the most important in determining their outcome [8]. Therapy should not be unnecessarily delayed, nor should a suboptimal treatment programme be given. Managers and patients must understand that simply reducing the standard dosage administered or the number of courses given to save costs is unacceptable. For tumours sensitive to chemotherapy a combination of drugs, each employed at an optimal dose, is more likely to induce tumour response and result in meaningful benefit. The treatment of patients with a minimal tumour burden is usually more effective. The results of numerous clinical trials in recent years clearly demonstrate that certain patient groups with operable breast [9] and colorectal cancer [10] survive longer when given systemic therapy after tumour resection. The implications of these new data are that a large number of additional patients may benefit from chemotherapy. Recently several high cost drugs have been marketed for common cancers. Although capable of a significant response rate in patients with metastatic disease, such responses are often of short duration and may only prolong median survival by a few weeks to months. To what extent some of these new drugs should replace older and cheaper agents has not yet been determined in well designed trials with relevant endpoints including cost benefit assessment. Prioritisation must be based on the relative efficacy and cost effectiveness of specific drugs [11]. Inevitably this will have a subjective element and will vary with the overall allocation to cancer treatment in a country.

Tumour categories

There are more than 200 types of cancer and these respond variably to chemotherapy. Tumours can be usefully split into five categories with regard to the relative usefulness of chemotherapy. This provides a basis for examining the overall health gain of defined interventions.

Category 1. Tumours for which there is evidence that the use of a single or a combination of drugs used alone or with other therapeutic modalities will result in cure as defined by a normal life-span in some and a prolongation of survival in most patients.

Category 2. Tumours where the average survival is prolonged when chemotherapy is used as an adjuvant to local surgery or radiotherapy in early stages of disease.

Category 3. Tumours for which there is evidence that the use of one drug or a combination of drugs will cause tumour shrinkage in more than 20% of selected patients with metastatic disease with almost certain improvement in the quality of life. Prolongation of survival occurs in most of the responding patients but may be of short duration.

Category 4. Tumours where local control may be improved by the use of chemotherapy before, during or after surgery and radiotherapy.

Category 5. Tumours for which there are currently no effective drugs. Objective responses occur in less than 20% of patients and there is no evidence of survival benefit in randomised controlled trials when compared to best supportive care.

Table 1 divides the commonly occurring cancers into each of these five categories.

Table 1. Cancers grouped according to the effectiveness of chemotherapy and hormonal therapy.

Category 1, potentially curable even with systemic disease
- Germ-cell cancers
- Trophoblastic cancers
- Acute lymphoblastic leukaemia
- Acute myeloid leukaemia
- Acute promyelocytic leukaemia
- Hairy cell leukaemia
- Hodgkin's disease and non-Hodgkin's lymphoma

Category 2, adjuvant chemotherapy of established benefit in local disease
- Colo-rectal cancer (Dukes C)
- Breast cancer
- Ovarian cancer
- Osteosarcoma
- Ewing's sarcoma
- Neuroblastoma
- Retinoblastoma
- Soft tissue sarcoma
- Wilms' tumour

Category 3, palliative benefit only in metastatic disease
- Lung cancer
  - Small-cell – relatively long duration
  - Non-small-cell – relatively short duration
- Ovarian cancer
- Chronic lymphocytic and myelogeneous leukaemia
- Anal cancer
- Bladder cancer
- Endometrial cancer
- Prostate cancer
- Kaposi's sarcoma (non-HIV)
- Indolent AIDS-related lymphoma and Kaposi's sarcoma
- Adult soft tissue sarcoma
- Colorectal cancer
- Cervical cancer
- Head and neck cancer
- Oesophageal cancer
- Stomach cancer
- Breast Cancer

Category 4, local control enhanced
- Oropharyngeal cancer
- Nasopharyngeal cancer

Category 5, chemotherapy ineffective
- AIDS-related CNS lymphoma
- Hepatobiliary cancers
- Melanoma
- Pancreatic cancer
- Renal-cell cancer
- Thyroid cancer
- Central nervous system cancers

Prioritising anti-cancer drugs

We have banded anti-cancer drugs into three priority levels. The determination of the priority grouping of a drug is based on its utility in treating category 1, 2 and 3 tumours and the global incidence of the responding tumours. Table 2 shows the effects of systemic therapy in the treatment of the ten most common cancers worldwide. Unfortunately, good responses outside the adjuvant situation are limited for most of these tumours. We have identified 13 effective drugs which provide beneficial

Table 2. Effects of systemic therapy on the ten most common cancers worldwide.

Cancer	Category			
	1	2	3	5
Lung			+	
Stomach			+	
Breast		+	+	
Colorectal		+	+	
Cervix			+	
Head and neck			+	
Lymphoma	+	+	+	
Hepatobiliary				+
Oesophagus			+	
Prostate			+	

Table 3. Cancer drug priority list.

	Top 10 cancers	Category 1–2	Generic
Priority 1			
Bleomycin	+	+	+
Chlorambucil	+	+	+
Cisplatin	+	+	+
Cyclophosphamide	+	+	+
Doxorubicin	+	+	+
Etoposide	+	+	+
5-Fluorouracil	+	+	+
Methotrexate	+	+	+
Prednisolone	+	+	+
Procarbazine		+	+
Tamoxifen	+	+	+
Vincristine	+	+	+
Vinblastine	+	+	+
Cytarabine		+	+
Dactinomycin		+	+
Daunorubicin		+	+
6-Mercaptopurine		+	+
Together with two antiemetics – a dopamine receptor and a 5-HT_3 receptor antagonist as well as dexamethasone			
Priority 2			
Busulphan		+	+
Carboplatin		+	
Flutamide	+		
Folinic acid	+	+	
Interferon alpha		+	
LHRH analogues	+		
Melphalan			+
Megestrol acetate	+		+
Mitomycin C			+
Mitoxantrone	+	+	
Paclitaxel	+		
Vinorelbine	+		
Priority 3			
Aminoglutethimide	+		+
Anastrozole	+		
Altretamine			
BCNU, CCNU			+
Dacarbazine			+
Docetaxel	+		
Epirubicin	+	+	
Gemcitabine	+		
Ifosfamide			
Irinotecan	+		
Raltitrexed	+		
Topotecan			

Table 4. The WHO cancer priority ladder.

- Tobacco control.
- Infection control.
- Curable cancer programme.
- Effective pain control.
- Early detection strategy.
- Sample cancer registry.
- Healthy eating programme.
- Referral guidelines.
- Clinical care guidelines.
- Nurse education.
- National cancer network.
- Clinical evaluation unit.
- Platform technology focus for region.
- Clinical research programme.
- Basic research programme.
- International aid programme.

outcomes against certain common tumours (Table 3) with a further four drugs necessary for the treatment of leukaemia. Thus, 17 drugs can be considered in priority one and are thus essential. In preparing this list of drugs, evidence of benefit was accepted only from scientifically valid clinical research. This has permitted the rational selection of essential drugs from more than 100 commercially available preparations. All 17 are widely available as generic preparations of relatively low cost.

A second group of drugs is listed in priority 2. These have well documented benefits in certain clinical situations. They are not truly essential as either drugs from the priority 1 list can be used as substitutes or their effects are only palliative. Cheaper and simpler forms of palliation with radiotherapy or analgesics may be more appropriate in low resource environments. Few of these drugs are available as generic preparations. The taxanes have generated considerable public interest. A randomised controlled trial in the USA demonstrated a 13 month survival advantage for women treated with paclitaxel and cisplatin as first line chemotherapy for ovarian cancer when compared to cyclophosphamide and cisplatin [11]. This has been confirmed by a Canadian–European study [12]. Several studies are still in progress to verify these results. The additional cost of the taxane per quality adjusted life year (QUALY) has been calculated at US$2000 per patient [13]. Paclitaxel would therefore move into priority 1 group if its benefit is clearly reproducible. The use of paclitaxel as second or third line therapy is not cost effective with a cost per QUALY of over US$30,000. The LHRH analogues are useful in palliating metastatic prostate cancer [14]. Although effective, they are costly and require frequent clinic attendances. Prostate cancer is dramatically increasing in incidence globally due to ageing populations. An oral formulation could change the priority category.

Many of the drugs in the priority three group are recent, expensive and of low effectiveness. About half of patients with metastatic breast cancer respond to docetaxel. The side effects are significant and the median response duration is only five to six months [15]. Altretamine [16] and topotecan [17] are being marketed for advanced ovarian cancer; gemcitabine for non small cell lung cancer [18] and irinotecan for colorectal cancer [19]. With all these agents, the response rate is low and of short duration, and there are significant side effects. There has been an increasing trend for manufacturers to disseminate positive information about their anti-cancer drugs through press releases and by using local public relations firms. In this way, demands are created which can disturb the financing of a logical cancer priority ladder (Table 4). Education of political decision makers as well as the public is essential to correct this imbalance.

There are many drugs currently in clinical trial. These include complex pharmaceuticals such as cytokines, anti-angiogenesis agents, growth factor inhibitors, monoclonal antibodies, vaccines and gene therapy [20]. There is no doubt that the recent molecular revolution will result in novel strategies to selectively destroy cancer cells. However, aggressive public relations activities by biotechnology companies, universities and cancer charities has led to a significant but as yet unfulfilled public expectation. Patients and their families need to be made aware of the experimental nature of such therapies and the high chance of failure of early studies. Enhanced public education is required to explain the complexities of new cancer drug investigation.

High-dose therapy

There is compelling evidence for a strong relationship between dose intensity of chemotherapy and tumour response rate [21]. The development of recombinant bone marrow colony stimulating factors has promoted the use of high dose marrow toxic drug regimens some of which involve either autologous bone marrow or peripheral blood stem cell rescue. Despite many publications in this area firm evidence of effectiveness has only been reported for certain leukaemias and relapsed lymphomas. Data from randomised clinical trials are still needed for other tumours and all such patients should be encouraged to participate in such a study. The high direct and indirect costs of such therapy together with its huge consumption of expertise, precludes its appropriateness in low resource environments where essential drugs are often lacking [22].

Supportive care drugs

Most effective cancer chemotherapy has significant side effects. Emesis and bone marrow damage predisposing to life threatening sepsis, may be reduced by pharmacological intervention. Cancer patients frequently develop other problems requiring drug therapy not due to medication.

Effective antiemetics are now available and should be administered routinely in advance with most chemotherapy combinations. We classify the availability of steroids, a dopamine receptor antagonist (domperidone, metoclopramide, prochlorperazine) and a 5-HT_3 recep-

tor antagonist (granisetron, ondansetron, tropisetron) as essential. There is no convincing evidence that any particular agent in either of these groups of drugs is preferred [23]. Local price should thus be the major determinant of choice. 5-HT_3 antagonists are clearly more justified in those patients receiving highly emetogenic regimens such as those containing cisplatin.

Neutropenia and the risk of infection is one of the most common dose limiting side effects of cancer chemotherapy, leading to reduced dosages, delayed cycles and reduced effectiveness. Recombinant colony stimulating factors (CSF) are available, which mobilise marrow stem cells – filgrastim, lenograstim and molgrastim. There is no good evidence that their routine use enhances the overall effectiveness or safety of standard dose chemotherapy [24] and so these agents are not classified as essential. These drugs are also used to generate stem cells to salvage patients after high-dose chemotherapy. Anaemia can be treated with blood transfusion. The use of recombinant erythropoietin is therefore not essential.

A wide range of relatively cheap drugs are available for the relief of a range of symptoms experienced by cancer patients [25]. Especially important are the opioid analgesics which are often strictly controlled and essentially unavailable in effective quantities in many countries. Education of politicians, legislators and health care professionals is necessary to reduce the immense amount of unecessary suffering caused by inadequate analgesic use [26].

Chemotherapy delivery

The organization of chemotherapy delivery services has dramatically altered over the last ten years. Most drugs, even in complex regimens, are now given in the outpatient setting rather than in a hospital ward. This has resulted in the concept of nurse led chemotherapy day care suites, where specially trained nurses supervise the administration of chemotherapy and in some countries can now prescribe supportive care drugs [27]. Centralising chemotherapy services creates considerable savings by reducing wastage and allowing the development of coordinated drug policies [28]. Day care is preferred by patients and their carers. The WHO strongly supports the development of nurse led day chemotherapy suites in all hospitals dealing with cancer patients.

Conclusion

The epidemiology of cancer in various settings and differing local health priorities means that individual requirements for cancer drugs will vary. Nevertheless the essential drug concept can be applied using the priority banding described. It is vital to continually assess the overall effectiveness of available drugs in the light of new clinical trial data. A curable cancer programme is a useful tool for political persuasion by taking positive action against the disease. It forms a major part of the WHO cancer priority ladder for effective cancer control (Table 4). Research is urgently needed in simplifying regimens for use in geographically disperse poor areas. The establishment of rigorous audit and assessment strategies will enhance the cost effectiveness of chemotherapy. The introduction of an analytic culture even in low resource settings provides the basis for future clinical research programmes [29]. The pharmaceutical industry have found it difficult to implement a price banding system in which poorer countries obtain drugs at lower prices. Parallel importing by wholesalers simply shifts the drugs obtained more cheaply back to the richer countries with profits taken by those involved at each step of the process. Establishing an essential drug list and monitoring the availability of its components will help to improve the global quality of cancer care.

References

1. World Health Organization. National Cancer Control Programmes. Policies and Managerial Guidelines. Geneva: WHO 1995.
2. Sikora K. Developing a global strategy for cancer. Eur J Cancer 1999 (in press).
3. Stiller C. Centralised treatment, entry to trials and survival. Br J Cancer 1994; 70: 352–62.
4. World Health Organization. Essential Drugs for Cancer Chemotherapy: Memorandum From a WHO Meeting. Bulletin of the WHO 1985; 63: 999–1002
5. WHO Consultation. Essential Drugs for Cancer Chemotherapy. Bulletin of the World Health Organization 1994; 72: 693–8.
6. Sobin LH, Fleming ID (eds). TNM Classification of Malignant Tumours, 5th edition. Geneva: UICC 1997.
7. Benjamin I, Glodwein JW, Rubin SC et al. Oncolink: A cancer information resources for oncologists and the public on the internet. Gynecol Oncol 1996; 60: 8–15.
8. Karjalainen S, Palva I. Do treatment protocols improve end results. BMJ 1989; 299: 1069–72.
9. Early Breast Trialist's Collaborative Group Systematic treatment of early breast cancer by hormonal, cytotoxic or immune therapy. Lancet 1992; 339: 1–15.
10. Fuchs CS, Mayer RJ. Adjuvant chemotherapy for colon and rectal cancer. Semin Oncol 1995; 22: 472–87.
11. McGuire WP, Hoskins WJ, Brady MF et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and IV ovarian cancer. N Engl J Med 1996; 334: 1–6.
12. Piccart MJ, Bertelsen K, Stuart G et al. Is cisplatin–paclitaxel standard in first-line treatment of advancerd ovarian cancer? Proc Am Soc Clin Oncol 1997; 16: 3 (Abstr 1258).
13. McGuire W, Neugut A, Arikaian S et al. Analysis of the cost effectiveness of paclitaxel as an alternative combination therapy for advanced ovarian cancer. J Clin Oncol 1997; 15: 640–5.
14. Debruyne FM, Dijkman GA. Advances and trends in hormonal therapy for advanced prostate cancer. Eur Urol 1995; 28: 177–88.
15. Anonymous. Paclitaxel and docetaxel in breast and ovarian cancer. Drug Ther Bull 1997; 35: 43–6.
16. Rustin GJ, Nelstrop AE, Crawford M. Phase II trial of oral altretamine for relapsed ovarian carcinoma. J Clin Oncol 1997; 15: 172–6.
17. Creemers GJ, Bolis G, Gore M et al. Topotecan, an active drug in the second-line treatment of epithelial ovarian cancer. J Clin Oncol 1996; 14: 3056–61.
18. Bunn PA. The emerging role of gemcitabine in lung cancer. Semin Oncol 1997; 24: S7-1.

19. Bertino JR. Irinotecan for colorectal cancer. Semin Oncol 1997; 24: S18-3.
20. Sikora K. Gene therapy in developing countries. Gene Ther 1998; 5: 3–4.
21. Frei E, Cannellos GP. Dose, a critical factor in cancer chemotherapy. Am J Med 1986; 69: 585–9.
22. Waters TM. Economic analysis of new technologies: the case for stem cell therapy. J Clin Oncol 1997; 15: 2–4
23. Roila F, Ballatori E, Tonato M et al. 5-HT_3 receptor antagonists: Differences and similarities. Eur J Cancer 1997; 33: 1364–70.
24. Baldini E, Tibaldi C, Lencioni M et al. Filgrastim and lack of support of intensive adjuvant chemotherapy for high risk breast cancer patients. Am J Clin Oncol 1997; 20: 169–72.
25. World Health Organization. Symptom Relief in Terminal Illness. Geneva: WHO 1998.
26. World Helath Organization. Cancer Pain Relief. With a Guide to Opioid Availability. Geneva: WHO 1998.
27. Courtenay M, Butler M. Nurse prescribing – the knowledge base. Nurs Times 1998; 94: 40–2.
28. Esparza DM, Young N, Luongo JA. Effective planning for office and outpatient chemotherapy administration. Semin Oncol Nurs 1989; 5: 8–14.
29. Monographs. Integrating Economic Analysis into Cancer Clinical Trials – American Society of Clinical Oncology Economics Workbook. J Natl Cancer Inst 1998; 24.

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