Update / Le point

Essential drugs for cancer chemotherapy*

WHO Consultation[1]

The WHO recommendation on essential drugs for cancer chemotherapy has been updated. General principles on the proper role of cancer chemotherapeutic agents in relation to efficacy and on the classification of tumours with respect to their curative potential are discussed. Curable cancers and those cancers where the cost-benefit ratio clearly favours drug treatment can be managed appropriately based on only 24 drugs. Fourteen of them should ideally be available for the treatment of the ten most common cancers, 8 others should be available only where the resources and facilities exist for the treatment of paediatric tumours and leukaemias, and two drugs were recommended for the treatment of tumours for which there is good evidence that systemic treatment will palliate symptoms but not substantially prolong survival. The adoption of these recommendations should result in considerable reduction in both the mortality and morbidity from cancer throughout the world.

Introduction

Cancer is an important cause of morbidity and mortality worldwide. Each year, 9 million new cancers are detected and 5 million people die of it. Many cancer patients, if diagnosed at an early stage and given appropriate treatment, are cured and the remainder can be palliated for varying periods. To achieve these results, it is necessary judiciously to use surgery, radiotherapy, cytotoxic and endocrine therapies as well as appropriate supportive care including analgesics, antibiotics, and blood products (*1*, *2*).

Cancer treatment services, including chemotherapy, are an essential component of a national cancer control programme (NCCP). These programmes offer a rational mechanism for implementing existing knowledge on primary prevention, early diagnosis, screening, optimal treatment services and symptom control (*3*). The formation of an NCCP is, therefore an important health priority. 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 specialized facilities for optimal care. For example, therapy for children's cancers and for acute leukaemia in adults is best given in a centre capable of caring for the special needs of these patients (*4*, *5*). Unless appropriate resources and facilities are available, it may be inappropriate for a health care authority to acquire drugs which are required only to treat these cancers.

Cancer chemotherapy now joins surgery and radiation therapy as an essential component of modern cancer care (*6*). Medical staff must have appropriate training, knowledge and access to the requisite facilities to deliver and monitor chemotherapy. Increasingly, chemotherapy is an essential component of an effective multidisciplinary cancer treatment programme (*7*). A properly directed and integrated team approach with experts in at least pathology, surgery, radiation therapy and medicine is essential for optimal therapy at an acceptable cost.

To assist the WHO Expert Committee on the Use of Essential Drugs in their selection of drugs for cancer chemotherapy, WHO invited medical oncologists from Africa, North America, Asia, Australia and Europe to review the essential drugs list for can-

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cer which had been formulated in 1983 (*8*). Their proposals and recommendations are described in this article.

General principles

Prior to the initiation of any cancer treatment, the goal of therapy must be realistically defined. Although a particular tumour type may be curable in some instances, not all patients with that tumour type will be cured and individual prognostic factors should be determined, including the stage (extent) of disease, the sites of metastases, the particular histology of the tumour, the functional status of vital organs, the nutritional status of the patient, the patient's willingness to accept the toxicity of the therapy, and the availability of necessary facilities and medical personnel to treat any complications arising from the treatment. In most cases cancer chemotherapy requires some access to laboratory facilities to monitor white blood cell and platelet counts. In addition, assessment of tumour response must be made at appropriate intervals to determine if it is in the patient's best interest to continue therapy.

Some principles of chemotherapy are well established. First, the initial therapies employed are often the most important in determining their outcome. Therapy should not be unnecessarily delayed, nor should a suboptimal treatment programme be given. 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 (*9*). Second, treatment of patients with a minimal tumour burden is usually more effective. The results of numerous clinical trials in recent years clearly demonstrate that patients with operable breast and colorectal cancer survive longer when given systemic therapy after tumour resection (*10, 11*). The implications of these new data are that a vast number of additional patients may benefit from, and therefore require chemotherapy.

Tumour categories

There are more than 100 types of cancer and these respond variably to chemotherapy. For example, cancers in children are generally very responsive to chemotherapy while many cancers in adults are less so. It is convenient to group malignancies according to the utility of chemotherapy. As described below, tumours have been placed in three categories.

Category 1

Tumours (listed below in alphabetic order) for which there is evidence that the use of one drug or a combination of drugs, alone or in conjunction with other therapeutic modalities, will result in a significant prolongation in the survival of at least some patients with this tumour type. For tumours marked with an asterisk, survival is prolonged only when chemotherapy is used as an adjuvant to local therapy in early stages of the disease.

Breast cancer; colon cancer (Dukes C)*; germ-cell cancers; gestational/trophoblastic cancers; Kaposi's sarcoma (aggressive); leukaemia—acute lymphoblastic, acute non-lymphoblastic leukaemia (AML), and hairy cell; lymphoma—Hodgkin's disease and non-Hodgkin's; multiple myeloma; osteosarcoma*; ovarian cancer (epithelial); paediatric—Ewing's sarcoma*, neuroblastoma (age <2 years), retinoblastoma*, soft tissue sarcoma, and Wilms' tumour; rectal cancer (Duke B2 & C)*; small-cell lung cancer.

Category 2

Tumours (listed below in descending order of relative chemosensitivity) for which there is evidence that the use of one drug or a combination of drugs will cause tumour shrinkage and almost certain improvement in the quality of life. Marginal prolongation of survival *may* occur as well, but this is not established. Tumours sensitive to endocrine therapy, but not sensitive (or only very marginally responsive) to cytotoxic treatment are noted with a double asterisk. For tumours marked with a dagger (†), benefits have been clearly established only when chemotherapy was used in early stages of the disease.

Chronic lymphocytic leukaemia; chronic myelogeneous leukaemia; anal cancer†; bladder cancer (intravesicular therapy)†; endometrial cancer**; prostate cancer**; Kaposi's sarcoma (non-HIV), indolent; AIDS-related lymphoma and Kaposi's sarcoma; paediatric neuroblastoma (age >2 years); adult soft tissue sarcoma; colon cancer (metastatic); cervical cancer; nasopharyngeal cancer; head and neck cancer; oesophageal cancer†; bladder cancer (systemic therapy); central nervous system cancers**.

Category 3

Tumours (listed below in alphabetic order) for which there are no effective drugs. Although some drugs may have been shown to shrink these tumours, the effect is so marginal that it is unlikely the patient will have an improvement in the quality of life except in extremely rare instances, and it is likely that the majority of patients will have their quality of life compromised and possibly their survival shortened as a result of chemotherapy.

AIDS-related CNS lymphoma; oesophageal cancer (metastatic); gastric cancer; hepatobiliary cancers; melanoma; non-small-cell lung cancer; pancreatic cancer; renal-cell cancer; thyroid cancer.

Table 1: **Effects of systemic therapy in the treatment of cancer**

	Prolonged survival	Palliation	None
Ten most common cancers worldwide:[a]			
1. Lung cancer:			
Non-small cell types			X
Small-cell type	X	X	
2. Gastric cancer			X
3. Breast cancer	X	X	
4. Colorectal cancer:			
Metastatic		X	
Colon cancer (Dukes C)	X[b]		
Rectal cancer (Dukes B2 & C)	X[b]		
5. Cervical cancer		X	
6. Head and neck cancer		X	
Nasopharyngeal cancer		X	
7. Lymphoproliferative diseases:			
Hodgkin's disease	X	X	
Non-Hodgkin's	X	X	
Multiple myeloma	X	X	
AIDS lymphoma		X	
AIDS CNS lymphoma			X
8. Hepatobiliary cancers			X
9. Oesophageal cancer:			
Early		X[c]	
Metastatic			X
10. Prostate cancer		X[d]	
Other tumour types (alphabetically):			
AIDS-related Kaposi's sarcoma		X	
Anal cancer		X[c]	
Bladder cancer:			
Intravesicular therapy		X[c]	
Systemic therapy		X	
Central nervous system cancers		X[d]	
Endometrial cancer		X[c]	
Germ-cell cancers	X	X	
Gestational/trophoblastic cancers	X	X	
Kaposi's sarcoma			
Non-HIV, indolent		X	
Aggressive	X	X	
Leukaemia:			
Acute lymphoblastic	X	X	
Acute non-lymphoblastic (AML)	X	X	
Chronic lymphocytic		X	
Chronic myelogenous		X	
Hairy cell	X	X	
Melanoma			X
Osteosarcoma	X[b]	X	
Ovarian cancer (epithelial)	X	X	
Pancreatic cancer			X
Paediatric:			
Ewing's sarcoma	X	X	
Neuroblastoma (age <2 years)	X[b]	X	
Neuroblastoma (age >2 years)		X	
Retinoblastoma	X[b]	X	
Soft tissue sarcoma	X	X	
Wilms' tumour	X	X	
Renal cell cancer			X
Soft tissue sarcoma (adult)	X		
Thyroid cancer			X

[a] In descending order of frequency.
[b] Survival prolongation achieved only when systemic therapy is used as an adjuvant to local therapy.
[c] Benefit (primarily a prolongation of disease-free survival) clearly established only when chemotherapy is used in early stages of the disease.
[d] Benefits achieved from the use of endocrine therapy.

Essential drugs

The effects of systemic therapy—prolonged survival, palliation, or no effect— in the treatment of the ten most common cancers worldwide, and on other tumour types are shown in Table 1.

Effective drugs have thus been identified which provide beneficial outcomes against certain tumours (Table 2). The first 14 drugs on this list are those needed to treat the ten most common cancers in the world. In addition, to treat all paediatric tumours for which systemic therapy has been established to prolong survival (category 1), an additional six drugs are included. Another two drugs are in the list to treat adult leukaemias and adult lymphomas for which chemotherapy has been shown to prolong survival (category 1 tumours). Two additional drugs are needed to treat tumours (in category 2) for which there is good evidence that systemic treatment will palliate symptoms but not substantially prolong survival.

Thus, 24 drugs are now available which, when used singly or in combination, will result in considerable reduction in mortality and morbidity from cancer worldwide. In preparing this list of drugs and their indications (Table 3), evidence of benefit was accepted only from scientifically valid clinical research. This has permitted a rational selection of "essential" drugs from the more than 80 commercially available anti-cancer drugs (*12*).

Utilization and application

The epidemiology of cancer in various geographical settings and the different local health priorities mean that individual requirements for cancer drugs will differ. Nevertheless the categorization of cancers, as described above, provides a mechanism to estimate the impact of systemic treatment on cancer patient outcomes worldwide or regionally. The following points should be noted.

- As the list of drugs includes some agents that are effective only in patients with rare tumours, individual health authorities must weigh the relative costs of such therapies against the frequency of the condition.

• The treatment of cancers arising in AIDS patients is a special case. Chemotherapy regimens effective in the treatment of tumours arising in non-AIDS patients may also be effective in AIDS patients (e.g., non-Hodgkin's lymphoma, Kaposi's sarcoma), but these treatments rarely cause complete regression of the tumour and are associated with high attendant morbidity.

• Information on the administration, contraindications, and toxicity/adverse effects of these drugs, as well as precautions to be taken, is readily available from other sources and therefore not given here. It is, however, essential that this information should be available along with guidelines for multiagent therapy at all locations where cancer treatment is administered.

• Systemic therapy of patients with cancer is rapidly evolving with increasing emphasis on results from appropriately designed and evaluated clinical trials. Currently, promising data for several therapies are not yet definitive. Some topics worthy of reconsideration in the next few years may include:

— taxanes (e.g., Taxol ® or paclitaxel, drugs extracted from the yew) in ovarian and breast cancer (*13*);

— interferon-'alfa' in chronic myeloid leukaemia and as a surgical adjuvant in melanoma patients (*14, 15*);

— complete androgen blockade in prostate cancer (*16*);

— all-*trans*-retinoic acid (ATRA, tretinoin) in acute promyelocytic leukaemia (*17*);

— fludarabine in chronic lymphocytic leukaemia (*18*);

— haematopoietic growth factors in intensive chemotherapy programmes (*19*); and

— fluorouracil + calcium folinate as a surgical adjuvant in colorectal cancer.

The above will have to be evaluated in many areas of the world to identify possible regional variations. Meanwhile, health planners and local physicians could evaluate the present essential drugs list in their country, region or hospital.

Table 2: **List of essential drugs for treating the ten most common cancers worldwide and other tumours in categories 1 and 2**

		Useful in category 1			
	For treating 10 most common cancers	Paediatric tumours	Adult leukaemia and lymphoma	Other tumours	Useful in category 2
Bleomycin	X		X	X	
Cisplatin	X			X	
Cyclophosphamide	X	X	X	X	
Dacarbazine	X		X		
Doxorubicin	X	X	X	X	
Fluorouracil	X				
Calcium folinate	X				
Levamisole	X				
Mechlorethamine (mustine)	X		X		
Prednisone	X	X	X		
Procarbazine	X		X		
Tamoxifen	X				
Vinblastine	X		X	X	
Vincristine	X	X	X		
Cytarabine		X	X		
Dactinomycin		X		X	
Etoposide		X		X	
Asparaginase		X	X		
Mercaptopurine		X			
Methotrexate		X			
Cladribine (Chlorodeoxyadenosine)			X		
Daunorubicin			X		
Hydroxycarbamide (hydroxyurea)					X
Mitomycin					X

Table 3: **Twenty-four essential drugs for cancer chemotherapy and their indications**

	Tumours in:	
	Category 1	Category 2
Bleomycin*	Germ-cell cancers, Hodgkin's disease Kaposi's sarcoma (aggressive)	Nasopharyngeal cancer
Cisplatin*	Germ-cell cancers, gestational/trophoblastic, ovarian (epithelial), small-cell lung cancer	Bladder, cervix, œsophagus, head & neck, nasopharyngeal cancers
Cladribine (chlorodeoxyadenosine)	Hairy-cell leukaemia	
Cyclophosphamide*	Breast, Ewing's sarcoma, neuroblastoma, non-Hodgkin's lymphoma, ovarian (epithelial) paediatric soft tissue sarcoma, small-cell lung cancer	Chronic leukaemia (lymphocytic and granulocytic)
Cytarabine	Acute leukaemia (lymphoblastic and non-lymphoblastic), non-Hodgkin's lymphoma	
Dacarbazine*	Hodgkin's disease	
Dactinomycin	Ewing's sarcoma gestational/trophoblastic, Kaposi's sarcoma (aggressive), paediatric soft tissue sarcomas, Wilms' tumour	Kaposi's sarcoma (indolent)
Daunorubicin	Acute non-lymphoblastic or myelogenous leukaemia	
Doxorubicin*	Breast, Ewing's sarcoma, Hodgkin's disease, neuroblastoma, non-Hodgkin's lymphoma, osteosarcoma, paediatric soft tissue sarcoma, small-cell lung cancer	Adult soft tissue sarcoma, bladder cancer
Etoposide	Germ-cell cancers, small-cell lung cancer	
Fluorouracil*	Breast, colon, rectal cancers	Anal, cervic, colorectal (metastatic), œsophageal, head & neck, nasopharyngeal cancers
Hydroxyurea		Chronic granulocytic leukaemia
Asparaginase	Acute lymphoblastic leukaemia	
Calcium folinate*		Colorectal (metastatic)
Levamisole*	Colon cancer	
Mercaptopurine	Acute lymphoblastic leukaemia	
Mechlorethamine (mustine)*	Hodgkin's disease	
Methotrexate	Acute lymphoblastic leukaemia, breast cancer, gestational/trophoblastic, osteosarcoma	Bladder, head & neck cancers
Mitomycin C		Anal cancer
Prednisone*	Acute lymphoblastic leukaemia, Hodgkin's disease, multiple myeloma, non-Hodgkin's lymphoma	Central nervous system tumours
Procarbazine*	Hodgkin's disease	
Tamoxifen*	Breast cancer	Endometrial cancer
Vinblastine*	Germ-cell cancers, Hodgkin's disease, Kaposi's sarcoma (aggressive)	Kaposi's sarcoma* (indolent)
Vincristine*	Acute lymphoblastic leukaemia, Ewing's sarcoma, Hodgkin's disease, neuroblastoma, non-Hodgkin's lymphoma, paediatric soft tissue sarcoma, small-cell lung cancer, Wilms' tumour	

* These 14 drugs are needed to treat the ten most common tumours in the world. There is overlap in the drugs needed to treat Hodgkin's disease, and elimination of chlormethine (mustine) and procarbazine from the list would leave doxorubicin, bleomycin, vinblastine, and dacarbazine to treat Hodgkin's disease. However, the combination of chlormethine (mustine), vincristine, procarbazine, and prednisone is a less expensive and acceptable regimen for the treatment of Hodgkin's disease.

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