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New Chemotherapy Treatments in Advanced Cancer Patients

An Easily Applicable Evaluation of Clinical Efficacy and Cost–effectiveness

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Novel cytostatic drugs have recently been introduced to treat advanced cancer patients. Although of only modest efficacy, their use is widespread, considerably increasing treatment costs. An easily applicable method to assess their efficacy and cost-effectiveness is needed. We have documented new cytostatic drugs whose consumption increased by over 60% from January 1998 to December 2000 in patients with advanced or metastatic cancer of the colorectum, lung (non-small cell), breast, ovary or brain. A review of the literature yielded 17 treatments that included these agents. For each regimen, we recorded six efficacy variables [median survival time (MS), survival rate at 1 year, absolute risk reduction, time to progression, quality of life (QoL), and patients needed to treat (NNT)]. A four-point (A–D) efficacy (E) scale and a five-point (1–5) strength of evidence (SE) scale were applied. We obtained the cost differential of each regimen for a 4-week treatment, cost per extra month of MS, and cost per NNT. One combination was rated with A efficacy (MS > 9 months + improved QoL) and nine with D (no MS or QoL improvement); 12 studies presented good quality (grade 1–2) evidence. The QoL of patients was significantly improved in only two regimens. The average cost differential was 1 311 € (all new regimens except one showed higher cost); the average cost per extra month of MS was 6 415 €; and treatment cost per NNT was 87 767 €. Our method proved to be easy to apply, enabled comparisons with other treatments to be made and revealed that these very costly changes in clinical practice are not justified by available studies.

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The past few years have seen rapid changes in the treatment of locally advanced and metastatic cancer patients, largely due to the approval and incorporation into clinical practice of numerous new drugs that have shown promising results in preliminary investigations (1). Many of these new molecules have been derived from recent advances in our understanding of cancer biology, drug resistance mechanisms and pharmacodynamics. The novel mechanisms of action of these agents have prompted clinicians to explore their benefits (2).

The use of these drugs has widened the therapeutic offer to patients who, until a few years ago, received no chemotherapy treatments except in clinical trials, leading to an increase in the volume and intensity of the therapy applied. However, published clinical studies have generally shown only modest outcome improvements limited to certain patient groups (3–5), as confirmed by recently published reviews (6–8). Furthermore, results obtained in clinical trials often differ from those achieved in normal clinical practice, and the external validation process is hampered by differences in patient selection and by inequalities in care quality among different healthcare centres, especially in complex treatments (9, 10).

Two fundamental issues for clinicians in this field are the selection of patients for active therapy and the identification of the best treatment option. The choice of a treatment must be based on: the degree of certainty that it will yield a benefit, conditioned by the quality of supporting studies; the magnitude of this benefit (the efficacy and effectiveness); and the economic costs it generates (1, 11). There appears to be a consensus that treatments should produce an incremental survival of at least 3–4 months in at least 20% of patients treated, and that the quality of life (QoL) of patients should be improved or not worsened (3, 12).

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The important issue of the selection of treatments for this group of patients has been addressed in published agreements (3, 11, 12) regarding: 1) when active chemotherapy treatment should be offered outside a controlled clinical trial (CCT) setting; 2) how results should be measured to provide genuine information about improvements of value to the patient; and 3) how the economic factor should be evaluated in the choice between one specific treatment and another.

The economic issue is not without importance. As well as the cost of the new drugs themselves, costly supportive treatments (especially colony stimulating factors, erythropoietin, antibiotics and antiemetics) are also involved (13). The phenomenon of novel treatments that yield only modest outcome improvements and greatly increase costs is not exclusive to oncology. Unfortunately, it is widespread in many other fields of medical care (14–16). In accordance with the principle of justice in the deontological code, it is part of the clinician's responsibility to be concerned with promoting an efficient distribution of resources.

Our group resolved to develop a method by which we could evaluate the new cytostatic treatments prescribed to patients with locally advanced and metastatic cancer. It would: 1) assess the efficacy and cost of treatments; 2) use the best current evidence; and 3) be easy to apply, using information available at any healthcare centre. The resulting study aimed: 1) to compare the efficacy of novel chemotherapeutic agents with that of previously used drugs, measured by the improvements in patient survival and QoL reported in key published studies; and 2) to develop and apply a method of measuring cost-effectiveness that can be of value to clinicians in their decision making.

MATERIAL AND METHODS

Selection of cytostatics to be studied and their indications

We examined the clinical records of patients with locally advanced and metastatic cancers of the breast, lung (non-small cell), ovary, colorectum and brain treated at Virgen de las Nieves University Hospital (Granada, Spain) from January 1998 to December 2000. We identified the cytostatic drugs of recent introduction whose unit intake increased by 60% or more during this period (Table 1). Eleven drugs were selected for inclusion in the study. All had been introduced in our centre within the previous 4 years, except for vinorelbine (7 years previously).

The updated technical specifications of the drugs (official Ministry of Health information) provided the indications for which they were approved until the end of the study period. The indications for their use at the hospital were supplied in writing by the clinical departments, and clinicians were interviewed for further clarification when required. Indication data included: tumour localization, histology and stage; line of treatment (first, second, third); patient subgroups, if appropriate; and complete administration regimen (dose, route, periodicity, number of cycles and association with other drugs).

Table 1

Drugs showing an increase in unit consumption of over 60% from January 1998 to December 2000

Active principle	% Increase in unit consumption
Oxaliplatin	1633
Vinorelbine	241
Gencitabine	203
Irinotecan	198
Topotecan	168
Docetaxel	166
Paclitaxel	103
Trastuzumab	100
Temozolamide	100
Doxorubicin (liposomes)	100
Raltitrexed	67

Reference search

Three types of reference search were carried out. Clinical departments were asked for information about the studies that had supported their decision to prescribe the new drugs, for each indication. The following databases were used: Medline, Cancerlit, Drugdex (Micromedex), Iowa Drug Information Service (IDIS), LMS alerts and PharmacoEconomics (ADIS International), and the Cochrane Library, in collaboration with the Andalusian Centre for Information on Medication (CADIME). We used the search strategy proposed by McKibbon et al. (17), which centres on the drug in question and on the clinical situation of interest. The search aimed to identify key studies rather than exhaustively review all related research. When we found no studies of adequate quality for a given regimen, the pharmaceutical laboratory was asked to supply the pivotal study that supported its approval. For each regimen, we selected the study that presented the best outcomes and provided adequate quality of evidence, when available.

Outcome evaluation: efficacy and strength of evidence scales (Table 2)

Our assessments of the efficacy of the treatment regimens and the quality of evidence supporting them were based on the four-point (A–D) efficacy (E) and five-point (1–5) strength of evidence (SE) scales proposed by Ferguson et al. (1). We modified the latter scale, because of the scarcity of meta-analyses for drugs of such recent introduction. Thus, a randomized CCT with adequate sample size was also given a rating of 1 (best evidence).

For each study, we recorded differences (with statistical significance and confidence interval, if reported) between the standard and novel regimen in the following outcome variables: 1) median survival (MS) in months; 2) survival at

Table 2

Efficacy (E) and strength of evidence (SE) scales

Efficacy[1]
A Prolongation of MS of >9 months and QoL improvement
B Prolongation of MS of 3–6 months and QoL improvement
C QoL improvement with no change in MS
D No impact on MS and minimal impact on QoL
Strength of evidence scale[2]
1 Meta-analysis or at least a randomized CCT with sample of >300 patients
2 Randomized CCT with sample of <300 patients and supported by Phase II study data
3 One or more Phase II studies published in indexed journals
4 One Phase II or III study published as conference abstract or internal drugs company information
5 Other sources

Abbreviations: MS = median survival; QoL = quality of life; CCT: controlled clinical trial.
[1]Taken from Ferguson (1).
[2]Taken from Ferguson (1), with modifications.

1 year, that is in the proportion of patients alive at 1 year, denoted as absolute risk reduction (ARR); 3) the number of patients needed to treat (NNT) for one more patient to survive to 1 year, obtained by dividing 100 by the ARR of survival at 1 year; this parameter was only calculated for treatments that produced a significant improvement in MS or QoL; 4) time to progression (TP) from onset of treatment (in months); and 5) QoL, when this parameter was formally and explicitly measured in the study.

Economic evaluation

We only calculated the cost to the hospital of the cytostatic drugs themselves. The following parameters were obtained:

1) *Cost differential* (CD) or difference in the direct cost per patient of a 4-week cytostatic regimen between the previously used (standard) and novel treatments. The calculation was based on hospital prices in 2000.
2) *Costs per positive event or cost per patient who survives more than 1 year (cost per NNT)*, considered as the result of multiplying the value of NNT by the cost differential and the TP of the new regimen, assuming that the patients undergo chemotherapy until the progression of the disease. This parameter was only collected in cases where there was a significant increase in the survival rate at 1 year.

$$\text{NNT cost} = \text{NNT} \times \text{CD} \times \text{TP}$$

3) *Costs per month of increase* in median survival or *incremental cost-effectiveness*. Defined as the cost of an additional efficacy unit, which in our case is the cost per month of increase in median survival, obtained when applying:

$$\Delta\text{CMS} = \text{CD} \times \text{TP}/(\text{MSn} - \text{MSs})$$

where MSn and MSs are the median survivals of the new and standard treatments, respectively. The possible cost of treatments administered after the failure of these regimens was not taken into account. The incremental cost-effectiveness was only calculated for treatments that yielded a significant increase in the median survival.

RESULTS

Our search strategy yielded one study that we considered the best for each of 17 treatment regimens for cancers in the studied localizations (Table 3), comprising 10 first-line regimens and seven second-line treatments.

Only one drug combination (paclitaxel and platinum in ovarian cancer) showed grade A efficacy (MS > 9 months), whereas nine regimens were rated with grade D efficacy level (no improvement in MS or QoL). The efficacy of the three remaining regimens could not be measured, because the studies only reported the rate of response or the toxicity. For 14 regimens, a published study was found in an indexed journal (SE scale 1, 2 or 3). Of these, 12 studies were considered of adequate quality (SE 1 or 2), that is CCTs with samples of more than 300 (SE 1, 10 studies) or less than 300 patients (SE 2, two studies). QoL was explicitly measured for nine out of the 17 regimens. The QoL was better with the new versus the standard regimen in only two cases (temozolamide in glioblastoma multiforme and docetaxel in non-small cell lung cancer) (marked in Table 3 with a plus sign). Thus, only one in six of the new drug regimens showed any evidence of QoL improvement.

Adequate information was available to apply these measurements to seven of the 17 regimens but not to the remaining 11, whose outcomes were not compared with those of another treatment regimen or showed no significant improvement. The results by tumour localization were as follows (Table 4).

Colorectal cancer (18–20). The three new drugs (irinotecan, raltitrexed and oxaliplatin) were first-line treatments. They were compared with a conventional 5-FU or Tegafur (UFT)+leucovorin regimen. The three corresponding studies provided a high quality of evidence (SE = 1). Only the combination with irinotecan increased the MS (from 14.1 to 17.4 months) and survival rate at 1 year (70% vs. 59%). The additional cost of each additional month was 2 145–2 498 €. For each extra patient surviving at 1 year, the increase in cost of the cytostatic drugs was 66 000–78 131 € versus standard regimens. The other two novel regimens cost more and were less effective, and one of them, the combination with oxaliplatin, was much more toxic. QoL was explicitly measured in all three studies but appeared to improve only with the irinotecan regimen.

Table 3

Summary of efficacy of regimens analysed and strength of evidence

		No.	Efficacy[1]					QoL	Strength of evidence				
			A	B	C	D	?		1	2	3	4	5
Colorectum (18–20)	First-line	3		1		2		3	3				
Non-small cell lung (21–25)	First-line	4				4		3	3	1			
	Second-line	1			1			1+	1				
Breast (26–30)	First-line	2		1			1*		1			1	
	Second-line	3			1	1	1*		1		1	1	
Ovary (31–33)	First-line	1	1						1				
	Second-line	2				2		1		1		1	
Brain (34–36)	Second-line	1			1			1+			2		
	Total	17	1	2	3	9	2	9++	10	2	2	3	

Abbreviation: QoL = quality of life.
+, significant difference; *, not comparative studies and studies with explicit measurement of quality of life.
[1]Scale taken from Ferguson (see Table 2 and reference 1).

Non-small cell lung cancer (21–25). We analysed one second-line and four first-line regimens. The five supporting articles offered SE 1 or 2 evidence but none of the regimens presented efficacy grades A or B. There was an appreciable improvement in QoL with the docetaxel regimen (second-line treatment) (E = C). With the exception of the latter regimen, all presented an increase in both toxicity and cost differential, which ranged from 624 € to 2 611 € per month. Each additional month of MS cost 3 078 € to 25 527 € per month (average of 11 276 €). Thus, the cost per additional year of life was 135 313 € (US$129 900). The cost of each patient that survived at 1 year was 12 020 € to 174 293 €.

Breast cancer (26–30). Two first-line and three second- or third-line (post-recurrence) regimens were studied. Three of the studies were rated with SE 1 and two with SE 3 and 4. One regimen (trastuzumab+paclitaxel) presented grade B efficacy but the QoL was not measured. Each additional month of MS cost an extra 2 404–6 612 € (average of 3 714 € per month) in cytostatic drugs with this regimen. Each year of life gained cost 44 565 € (US$42 782), and each patient who survived for more than 1 year cost between 48 080 € and 300 500 €.

Ovarian cancer (31–33). Three regimens were studied. The combination of paclitaxel+platinum increased the median survival by more than 9 months and the survival rate at 1 year was increased by 17% (efficacy of A but no QoL measurement). The other two regimens were less effective, and one of them lacked a full comparative study. Liposomal doxorubicin showed lesser adverse effects and the infusion of cisplatin+paclitaxel took 24 h. Each additional month of MS increased the drug cost by 1 721 € (20 650 € for each additional year of life) and each patient that survived to 1 year cost 33 730 €. Interestingly, topotecan presented the same efficacy as paclitaxel (second-line treatment) and was less costly.

Brain cancer (34–36). Temozolamide did not significantly increase the MS or the survival rate at 6 months and was more toxic, although it did improve the QoL (C/D effectiveness). Its use was supported by a phase II study (SE of 3). For this indication, each additional month of MS cost an extra 3 005 € and each patient that survived for more than 6 months cost around 36 060 €.

The average cost differential of the new regimens was 1 311 € per cycle (range 4 365 to −441 €). Only one regimen was less costly (topotecan versus paclitaxel as second-line regimen in ovarian cancer). When we analysed all of the regimens that significantly improved the MS (Table 5), survival rate at 1 year, or QoL, each increase in MS of 1 month cost an average of 6 415 € per month, i.e. 76 977 € per year. Each additional patient alive at 1 year costs an average of 87 767 €. When only regimens with A or B efficacy (increase in MS of at least 3 months) were considered, the average cost of a 1-month increase in median survival was 2 979 € (range 1 493–7 073 €), with an average cost per year of life gained of 29 982 €.

DISCUSSION

According to the present findings, these novel regimens provide very modest benefits to patients with locally advanced or metastatic cancers at the localizations studied, compared with standard treatments. Out of 17 drugs, only seven offered some improvement in outcomes, with 10% more patients surviving to 1 year and an increase in median survival of 1/2 months. Moreover, the QoL of patients was not necessarily improved. Only one regimen and indication (paclitaxel+platinum in ovarian cancer) showed a significant increase in survival and improvement in QoL. In addition, a higher toxicity was reported for most of the novel regimens studied.

The selection of variables for the evaluation of treatment benefits is of critical importance (37–41). The Ferguson scale appears to be of great practical utility because it considers both the quality of the study, that is the confidence that we can have that the treatment can (or

Table 4

Results of evaluation of efficacy and cost-effectiveness of new treatments for metastatic and/or locally advanced colorectal, non-small cell lung, breast, ovary and brain cancer

Standard treatment	New treatment	ARR	ΔMS	NNT	Efficacy level		Strength of evidence	Cost for 4 weeks of standard treatment	Cost differential	Cost/month ΔCMS	Cost per NNT	Commentary
		%	Months	Patients	QoL	Global		€	€	€	€	
5FU+LV 18	Irinotecan+5FU+LV (CR)	10	3.3	10	±	B	1	43.10	1036*–1216	1899–2468	69 802–81 436	Full examination Grade 3–4 toxicity increased
5FU+LV (19)	Raltitrexed (CR)				NS	D	1	43.10	538	–	–	Evaluation not applicable. NS in results
5FU+LV (20)	Oxaliplatin+5FU+LV (CR)				NS	D	1	43.10	1299.73	–	–	NS in survival and Grade 3–4 toxicity increased
Vinorelbine/ifosfamide (21)	Docetaxel second-line (L)	13	0.1	8	+	C	1	388.7/93.78	1289*–994	19 688–25 527	15 750–20 442	Full examination
Cisplatin+etoposide (22)	Paclitaxel+cisplatin (L)	8.1	2.3	14	NS	D	1	121.83	1264*–2611	2638–5450	84 941–175 420	Full examination
Mitomycin+ifosfamide+cisplatin (23)	Gemcitabine+cisplatin (L)				NS	D	1	92.77	624.12	–	–	Evaluation not applicable. NS in results. Increase in toxicity
Cisplatin+etoposide (24)	Gemcitabine+cisplatin (L)				NS	D	2	136.21	769.12	–	–	Evaluation not applicable. NS in results
Vindesine+cisplatin (25)	Vinorelbine+cisplatin				–	D	1	150.6	309	–	–	Only response and toxicity
Doxorubicin or epirubicin+cyclophosphamide or paclitaxel (26)	Previous+trastuzumab (B)	11	4.8	9	–	B	1	239.52–1757.33	923*–4365	1500–7093	64 800–30 6428	Full examination
Doxorubicin+cyclophosphamide (27)	Docetaxel+doxorubicin (B)				–	NA	4	63.68	1478.67	–	–	Not comparative study
	Vinorelbine+docetaxel (28) (B)				–	NA	3	1510.32	–	–	–	Not comparative study
Mitomycin (29)	Paclitaxel (B)				–	C	4	29.38	1727.31	–	–	Six months response
Mitomycin+vinblastine (30)	Docetaxel second-line (B)	15	2.7	7	–	D	1	40.29	1727	2550	53363	Full examination
Cisplatin+cyclophosphamide (31)	Paclitaxel+Cisplatin (O)	17	14	6	–	A	1	52.20	1339	1720	36140	Full examination Longer time for administration
Topotecan (32)	Doxorubicin liposomial (O)				–	D	4	1315.94	712.17	–	–	Response and toxicity. Lower toxicity
Paclitaxel (33)	Topotecan (O)				NS	D	2	1757.33	441.39	–	–	Evaluation not applicable. NS in results
Procarbazine (34)	Temozolamide (brain)	16	1.7	7	+ (35)	C/D	3	1.21	1703	3250	35812	Grade 3–4 toxicity increased

Abbreviations: ARR = absolute risk reduction; NNT = number of patients needed to treat for one more to survive to 1 year; ΔCMS = increase in median survival; NA = not applicable; NS = non-significant difference; * = two different doses; CL = colorectal; L = lung; B = breast; O = ovary.
Full examination: reference includes data for assessment of efficacy and cost.

cannot) produce a benefit, and the amount of this benefit. The survival rate at 1 year and the median survival rates (or their transformation into ARR) are currently recommended as end-point measurements in advanced cancer patients. The NNT proposed in this paper is a valuable combined measurement in this setting, because it can be easily communicated to the patient and can also be used to compare different treatment regimens (42). In our opinion,

Table 5

Summary of cost-effectiveness of the regimens studied

Level of efficacy	Regimen	Cost per extra month MS (€)	Cost per extra year of life (€)	Cost per NNT (€)
Efficacy A–D[1]	All[1]	6 415	76 977	87 767
Efficacy A–B[1]	Irinotecan + 5FU-LV in colorectum (B)	1 899–2 468	22 788–29 616	69 802–81 436
	Trastuzumab in breast (B)	1 500–7 093	18 000–85 116	64 800–306 428
	Paclitaxel + cisplatin in ovary (A)	1 720	20 640	36 140
	Mean A–B	2 736	33 157	111 239
Efficacy C–D[1]	Docetaxel in lung second-line (C)	19 688–25 527	236 256–306 324	15 750–20 422
	Paclitaxel + platin in lung (D)	2 638–5 450	31 656–65 400	84 941–175 480
	Docetaxel second-line in breast (D)	2 550	30 600	53 363
	Temozolamid in brain (C)	3 250	39 000	35 812
	Mean C–D	9 850	118 202	64 294

Abbreviations: MS = median survival; NNT = number needed to treat.
[1]Only regimens showing significant differences in MS, time to progression or quality of life were analysed.

the advantages of NNT outweigh the reservations expressed about its use to define results occurring after variable time periods (39). With the regimens studied here, the events of interest take place at 12 months (with only one such event at 6 months). Regarding QoL measurement, despite recent methodological (43, 44) and practical (45–47) efforts to develop this approach, less than 10% of CCTs have incorporated this outcome measure (40, 45). This proportion was higher (50%) in the studies considered here.

When we evaluated the best available studies supporting these therapeutic changes, using a scale that contemplates the above variables, we observed that the efficacy of the new regimens was very modest and in many cases non-existent. Moreover, the effectiveness, that is the outcomes in normal clinical practice, may be even worse. We also highlight the fact that, in practice, little consideration is given to QoL when a new regimen is indicated. Finally, 11 of the 17 studies did not provide adequate information because they were not comparative studies or phase II trials and focused only on response rate or toxicity. Despite this, these studies have been used to justify the treatment changes and the introduction of these drugs.

The increased cost of these new treatments is evident. The extra cost of each additional month of survival, when achieved, was an average of 6 415 € and the cost of each patient surviving to 1 year was about 87 767 €. Nevertheless, the three regimens rated with an efficacy of grade A or B showed a similar cost-effectiveness to that of other healthcare activities (48), with each additional year of life costing an average of 33 157 €. The modest efficacy of novel drugs used in advanced cancer patients in Europe and the significant increase in costs entailed were recently highlighted in a study by Garattini & Bertele (49).

Various authors have underlined the methodological difficulties of conducting economic evaluation studies in the clinical setting (50–52), where the economic issue is often considered secondary or even perverse (53, 54). Nonetheless, it seems clear that some economic information is necessary to ensure efficient clinical practice (55), especially in this type of patient. Importantly, it should be presented in a form that we can use when making clinical decisions. In short, we need economic data that can be incorporated into our clinical practice (1, 15). The definition of cost-effectiveness thresholds has always been a controversial issue and remains a matter of debate. Claxton et al. (56) recently described the contributions to decision-making that can be offered by cost-effectiveness studies that analyse the available evidence. In relation to oncology, reviews of published data have been reported to present the same limitations as noted in the present paper (57). Our proposed system is based on information that is available at each centre and only takes account of the costs of the cytostatic drugs. It is of particular relevance in the field of oncology, which has seen a net increase in the costs of caring for advanced cancer patients, largely attributable to increased drug (cytostatic and supportive) costs, which comprise 20 to 40% of the total (13, 41). In this review, we have laid special stress on the doubts about the efficacy of many treatment regimens. This information, alongside data on toxic effects, QoL impact and costs, can aid but not completely determine the decision-making process. The value of this approach lies in the quantification of the economic implications of treatments that yield little benefit.

As pointed out by Smith & Bodurtha (54), without efficacy, defined as the impact on survival or the significant reduction of morbidity, little can be said about cost-effectiveness. As resources are invariably limited, it can be argued that excessive spending on these drugs be used in the development of other healthcare services, such as palliative or psychological care.

Some limitations of our review should be taken into account. First, the quantity and quality of the information provided by the studies was sometimes inadequate to allow a full assessment of the efficacy. It was not always possible to obtain all of the data necessary to evaluate the methodological quality or statistical validity of the studies. A further limitation is that only the costs of the drugs were considered. Moreover, the comparability of this experience

at our particular hospital cannot be assured when the analysis is carried out at other centres. Our aim was not to obtain an exhaustive and complete economic evaluation of these drugs, but rather to make a clinically useful estimation based on available data. Nevertheless, comparisons can be established through the unit prices of the regimens considered to be standard. Moreover, from a clinical standpoint, it is possible to add more economic evaluation data by increasing or reducing costs according to toxicity data or substantial changes in the administration route. Thus, among the regimens evaluated in the present work, there was a significant increase in haematological toxicity (grade 3–4), febrile neutropenias, or episodes requiring hospitalization in four of the seven regimens for whom a complete evaluation was reported.

In many hospitals, the new regimens analysed here represent the habitual treatment for numerous patients in these clinical situations and are not limited to randomized and controlled trials. It appears evident that greater critical rigor should be applied to the evaluation of studies on new treatments, both by health authorities in approving novel cytostatic drugs for use in the public healthcare system and by clinicians themselves (54). In many cases, the decision to introduce a new drug must be taken by the Pharmacy Commission at each healthcare centre. The methodology presented in this review may help to increase the transparency and scientific rigour of decision-making and improve discussions between clinicians and administrators. This issue is of particular relevance at a time when patients are asked to take a much more active role in the selection of their treatment and require full information about the expected benefits (58).

REFERENCES

1. Ferguson JSJ, Summerhayers M, Masters S, Schey S, Smith IE. New treatment for advanced cancer: an approach to prioritization. Br J Cancer 2000; 83: 1268–73.
2. Beck WT, Dalton WS. Drug resistant mechanisms. In: De vita V, Hellman S, Rosemberg SA, eds. Cancer: principles and practices of oncology, 5th ed. New York: Lippincott; 1997. 498–508.
3. Ranghammar P, Brorsson B, Hygren P, Grimelins B. for the SBU-group. A prospective study for the use of chemotherapy in Sweden and assessment of the use in relation to scientific evidence. Acta Oncol 2001; 40: 391–411.
4. Khuri FR, Herbst RS, Fossella FV. Emerging therapies in non-small-cell lung cancer. Ann Oncol 2001; 12: 739–44.
5. Berrino F, Capocaccia R, Esteve J. (1999). Survival of cancer patients in Europe: The Eurocare Study II. IARC Scientific Publication no. 151. Lyon: International Agency for Research on Cancer.
6. Howe HL, Wingo PhA, Thun MJ et al. Annual report to the nation on the status of cancer (1973 through 1998), featuring cancers with recent increasing trends. J Natl Cancer Inst 2001; 93: 824–42.
7. Hoel DG, Davis DL, Miller AB. Trends in cancer mortality in 15 industrialized countries:1969–1986. J Natl Cancer Inst 1992; 84: 313–20.
8. Bailar JC. 3rd, Smith EM. Progress against cancer? N Engl J Med 1986; 314: 1226–32.
9. Rubens RD. Key issues in the treatment of advanced breast cancer. Pharm Econ 1996; 9: 1–7.
10. Nygren P, Glimelius B. for the SBU-group. The Swedish Council on Technology Assessment in Health Care (SBU). Report on cancer chemotherapy. Project objectives, the working process, key definitions and general aspects on cancer trial methodology and interpretation. Acta Oncol 2001; 40: 155–65.
11. NHS Cancer Plan. UK: Department of Health. September 2000. www.doh.gov.uk/cancer.
12. Norges Offentlige Utredningar. Care and knowledge. Norsk Kreftplan. 1997: 20 (quoted in 2).
13. Berenson R, Holuhan J. Sources of the growth in medicare physician expenditure. J Am Med Assoc 1992; 267: 687–91.
14. Evans DB, Tandon A, Murray Ch JL, Laner JA. Comparative efficiency of national health systems: cross national econometric analysis. Br Med J 2001; 323: 307–10.
15. Smith TJ, Hillner BE, Desch ChE. Efficacy and cost-effectiveness of cancer treatment: rational allocation of resources based on decision analysis. J Natl Cancer Inst 1993; 85: 1460–74.
16. Evans WK. A comparison with standard chemotherapy and best supportive care: cost-effectiveness of vinorelbine alone, vinorelbine plus cisplatin for stage IV NSCLC. Oncology 1998; 12: 3038–48.
17. McKibbon A, Eady A, Marks S. PDQ evidence-based principles and practice. Hamilton, Ontario: BC Decker Inc.; 1999.
18. Douillard JY, Cunninham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000; 355: 1041–7.
19. Cunningham D. Mature results from three large controlled studies with raltitrexed ('Tomudex'). Br J Cancer 1998; 77: 15–21.
20. Gramont A, Figer A, Seymour M, et al. Leucovorin and flurouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000; 18: 2938–47.
21. Fossella FV, DeVore R, Kerr R, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum containing chemotherapy regimens. J Clin Oncol 2000; 18: 2354–62.
22. Bonomi P, Kyung Mann K, Fairclough D, et al. Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group trial. J Clin Oncol 2000; 18: 623–31.
23. Crino L, Scagliotti GV, Ricci S, et al. Gemcitabine and cisplatin versus mitomycin, ifosfamide, and cisplatin in advanced non-small cell lung cancer: a randomised phase III study of the Italian Lung Cancer Project. J Clin Oncol 1999; 17: 3522–30.
24. Cardenal F, López-Cabrerizo MP, Antón A, et al. Randomized phase III study of gemcitabine—cisplatin versus etoposide—cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer. J Clin Oncol 1999; 17: 3522–30.
25. Le Chevalier T, Brisgand D, Soria JC, et al. Long term analysis of survival in the European randomized trial comparing vinorelbine/cisplatin to vindesine/cisplatin and vinorelbine alone in advanced non-small cell lung cancer. The Oncologist 2001; 6(Suppl 1): 8–11.

26. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001; 344: 783–92.
27. Naholtz JM, Falkson G, Chan S, (TAX306 group).. A phase III trial comparing doxorubicin and docetaxel to doxorubicin and cyclophosphamide as first line CT for MBC. Breast 1999; 8: 213.
28. Gasparini G, Caffo O, Barni S, et al. Vinorelbine is an active antiproliferative agent in pretreated advanced breast cancer patients: a phase II study. J Clin Oncol 1994; 12: 2094–101.
29. Dieras V, Marty M, Tubiana N, et al. Phase II randomized study of paclitaxel versus mitomycin in advanced breast cancer. Semin Oncol 1995; 22: 33–9.
30. Nabholtz J, Senn H, Bezwoda W, et al. Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 Study Group. J Clin Oncol 1999; 17: 1413–24.
31. McGuire VP. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996; 334: 1–6.
32. Gordon AN, Fleagle JT, Guthri D, Parkin DE, Gore M. Abstract ASCO 36th Annual Meeting Mayo 2000; 19: 380.
33. Ten Bokkel HW, Gore M, Carmichael J, et al. Topoptecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. J Clin Oncol 1997; 15: 2183–93.
34. Yung W. A phase II study of temozolamide vs procarbazine in patients with glioblastoma multiforme at first relapse. Br J Cancer 2000; 83: 88–93.
35. Yung WKA, Prados DM, Yaya-tur R. Temodal Brain Tumor Group. Multicenter phase II trial of temozolamide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. J Clin Oncol 1999; 17: 2762–71.
36. Osaba D, Brada M, Yung WKA, Prados M. Health-related quality of life in patients treated with temozolamide versus procarbazine for recurrent glioblastoma multiforme. J Clin Oncol 2000; 18: 1481–91.
37. Freedman LS, Granbard BI, Schatzkin A. Statistical validation of intermediate endpoints for chronic disease. Stat Med 1992; 11: 167–78.
38. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economics evaluations. Can Med Assoc J 1992; 146: 473–81.
39. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J. Natl Cancer Inst 2000; 92: 205–16.
40. Moinpour CM. Measuring quality of life: an emerging science. Semin Oncol 1994; 21: 48–63.
41. Karlsson G, Nygren P, Glimelius B. for the SBU-group. Economic aspects of chemotherapy. Acta Oncol 2000; 40: 412–33.
42. Lubsen J, Hoes A, Grobbee D. Implications of trial results: the potentially misleading notions of number needed to treat and average duration of life gained. Lancet 2000; 356: 1757–9.
43. Desch ChE, Benson AB III, Smith TJ, et al. Recommended colorectal cancer surveillance guidelines by the American Society of Clinical Oncology. J Clin Oncol 1999; 17: 1312–21.
44. Sackett DL, Richardson WS, Rosenbery W, Haynes RB. Evidence-based medicine. How to practice and teach EBM. London: Churchill Livingstone; 1997.
45. American Society of Clinical Oncology. Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. J Clin Oncol 1996; 14: 671–9.
46. Potosky AL, Harlan LC, Stanford JL, et al. Prostate cancer practice patterns and quality of life: the Prostate Cancer Outcomes Study. J Natl Cancer Inst 1999; 91: 1719–24.
47. Gunnars B, Nygren P, Glimelius B. for the SBU-group. Assessment of quality of life during chemotherapy. Acta Oncol 2001; 40: 175–84.
48. Buyse M, Thirio P, Carlson R, Burzykouwski T. for the Meta-Analysis Group in Cancer. Relation between tumour response to first line chemotherapy and survival in advanced colorectal cancer: a meta-analysis. Lancet 2000; 356: 373–8.
49. Garattini S, Bertele V. Efficacy, safety, and cost of new anticancer drugs. Br Med J 2002; 325: 269–71.
50. Aaronson NK. Quality of life research in cancer clinical trials: a need for common rules and language. Oncology 1990; 4: 59–66.
51. Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J. A rapid and systematic review of the effectiveness and cost-effectiveness of taxanes used in the treatment of advanced breast and ovarian cancer. Health Technology Assessment 2000; 4:(no. 17).
52. Dinnes J, Cave C, Huang S, Major K, Milne R. The effectiveness and cost-effectiveness of temozolamide for the treatment of recurrent malignant glioma: a rapid and systematic review. Health Technology Assessment 2001; 5:(no. 13).
53. Task Force on Principles for Economics Analysis. Economic analysis of health care technology. A report on principles. Ann Intern Med 1995; 122: 61–70.
54. Smith TJ, Bodurtha JN. Ethical considerations in oncology: balancing the interest of patients, oncologists and society. J Clin Oncol 1995; 13: 2464–70.
55. Slevin ML, Stubbs L, Plant HJ, et al. Attitudes to chemotherapy: comparing views of patients with those of doctors, nurses and general public. Br Med J 1990; 300: 1458–60.
56. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute for Clinical Excellence (NICE). Lancet 2002; 360: 711–5.
57. Cocquyt V, Moeremans K, Annemans L, Clarys P, Van Belle S. Long-term medical costs of postmenopausal breast cancer therapy. Ann Oncol 2003; 14: 1057–63.
58. Ravdin PM, Siminoff IA, Harvey JA. Survey of breast cancer patients concerning their knowledge and expectations of adjuvant therapy. J Clin Oncol 1998; 16: 515–21.