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Dossier

Chemotherapy of advanced epithelial cancer – a critical review*

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Summary – This article is a short version of a report which presents a comprehensive analysis of clinical trials and publications examining the value of cytotoxic chemotherapy in the treatment of advanced epithelial cancer. As a result of the analysis and the comments received from hundreds of oncologists in reply to a request for information, the following facts can be noted. Apart from lung cancer, in particular small-cell lung cancer, there is no direct evidence that chemotherapy prolongs survival in patients with advanced carcinoma. Except for ovarian cancer, available indirect evidence rather supports the absence of a positive effect. In treatment of lung cancer and ovarian cancer, the therapeutical benefit is at best rather small, and a less aggressive treatment seems to be at least as effective as the usual one. It is possible that certain sub-groups of patients benefit from the treatment, yet so far the available results do not allow a sufficiently precise definition of these groups. Many oncologists take it for granted that response to therapy prolongs survival, an opinion which is based on a fallacy and which is not supported by clinical studies. To date, it is unclear whether the treated patients, as a whole, benefit from chemotherapy as to their quality of life. For most cancer sites, urgently required types of studies such as randomized de-escalations of dose or comparisons of immediate *versus* deferred chemotherapy are still lacking. With few exceptions, there is no good scientific basis for the application of chemotherapy in symptom-free patients with advanced epithelial malignancy.

chemotherapy / carcinoma / overview

Résumé – La chimiothérapie du cancer épithélial avancé. Une revue critique. *Cet article est une version abrégée d'un rapport qui présente une analyse étendue d'études cliniques et de publications examinant la valeur de la chimiothérapie dans le traitement du cancer épithélial avancé. Comme résultat de l'analyse et des commentaires supplémentaires de la part d'un grand nombre d'oncologistes, nous pouvons retenir les faits suivants: À part le cancer du poumon, en particulier du type microcellulaire, il n'y a aucune preuve directe que la chimiothérapie prolonge la survie des patients ayant un carcinome avancé. À l'exception du cancer ovarien, les preuves indirectes existantes soutiennent plutôt l'absence d'un effet positif. Dans le traitement des cancers du poumon et des ovaires, le bénéfice thérapeutique est au mieux modeste et un traitement moins agressif paraît être aussi efficace que la thérapie habituelle. Il est possible que certains sous-groupes de patients bénéficient du traitement, mais les résultats disponibles ne permettent pas encore une définition suffisamment précise de ces groupes. Beaucoup d'oncologistes sont convaincus que la rémission de la tumeur prolonge la survie, opinion basée sur un faux raisonnement, et qui n'est pas mise en évidence par les études cliniques. Jusqu'à présent, il n'est pas clair que l'ensemble des patients doivent bénéficier de la chimiothérapie, en ce qui concerne la qualité de leur vie. Pour la plupart des cancers, il y a toujours un manque urgent d'études randomisées de certains types, comme par exemple les comparaisons avec des doses moindres ou la comparaison entre une thérapie immédiate et une thérapie reportée. À part quelques exceptions, il n'y a pas de fondement scientifique pour l'application de la chimiothérapie chez les patients ne présentant pas de symptômes.*

chimiothérapie / carcinome / revue

* This article is derived from a comprehensive report on the subject [1] to which the reader is referred for further details.

Introduction

Epithelial malignancies are responsible for more than 80% of cancer mortality in the world. In the Western industrialized countries they take a toll of over 1 million lives per year. Among others they include nearly all malignant tumors of trachea, bronchus, lung, stomach, colon, rectum, esophagus, breast, bladder, pancreas, ovary, cervix and corpus uteri, head and neck, and liver. Although reliable data on the treatment of advanced epithelial cancer seem to be unavailable, one can safely assume that the majority of patients receive some form of systemic cytotoxic therapy before death and that in virtually all cases such treatment is taken into consideration.

Ideally, the decision in favor of or against chemotherapy should be influenced only by the following questions. First, does the treatment prolong survival? Second, does it contribute to the patient's well-being, *ie*, to his or her quality of life? Here we will try to answer both questions.

Let us begin with the first. Both laymen and doctors who are not particularly familiar with clinical oncology are likely to regard this question as purely rhetorical and superfluous, for they will take it for granted that if a notoriously toxic and expensive treatment cannot cure, it must at least have a beneficial effect on the patient's prognosis. In fact, this opinion is supported not only by the incontestable, sometimes dramatic, success of chemotherapy achieved in some non-epithelial malignancies such as leukemia, Hodgkin's disease or highly malignant non-Hodgkin lymphoma, but also by assertions of positive results in epithelial cancer made in scientific publications or oncological textbooks as well as in communications intended for the public [6, 13, 21, 28, 43, 49, 62, 64, 94, 109, 112, 114, 127, 135]. These claims are largely based on the observation that survival rates have improved since the introduction of chemotherapy into routine practice at the beginning of the 1970s. Unfortunately, however, comparisons with historical controls tend to yield highly biased results, so that in general, they are inadequate for the assessment and quantification of therapeutic advances [14, 29, 39, 40, 102, 117, 126, 139]. Thus, the improvement of diagnostic techniques, the intensification of screening and self-observation, and the refinement of disease monitoring lead to earlier detection of the disease or metastasis, thus prolonging survival even if no real therapeutic progress has been made. Another phenomenon causing bias is stage migration which occurs because increasing diagnostic sensitivity shifts the distribution of stages to the more advanced ones. Paradoxically, this leads to an improvement of prognosis both in the early and the advanced stages. While the former ones are depleted of patients with advanced disease, the latter ones profit from the addition of patients with a relatively good prognosis. Further reasons for biased results in poorly controlled studies include differences in supportive care or in prognostic factors (due to different inclusion criteria or self-selection), and in methods or quality of observation and follow-up.

In order to render possible an assessment of the vast amount of published studies, it is useful to classify the evidence for or against beneficial treatment effects into direct and indirect ones. Direct evidence permits, within the bounds of statistical and methodological error implied by the study design, the conclusion that the hypothesized effect is present or absent. It always comes from a randomized study. There are three types of studies differing markedly in their intepretability and the strength of positive or negative outcomes:

i) Randomized comparisons of patients treated with the regimen or substance T in question, with controls receiving identical treatment with the omission of T. In particular, comparisons with untreated controls; ii) randomized comparisons of immediate *versus* deferred therapy, *ie* treatment started on symptoms only; iii) Randomized dose-effect studies.

Indirect evidence is obtained from studies in which differences of survival curves cannot be put down to successful treatment in the superior group. This applies to two classes of investigations:

i) Randomized comparisons of different chemotherapy regimens; ii) non-randomized comparisons of therapy groups.

See [1] for a discussion of the relative value of evidence from these studies. For what follows it suffices to note that if all pairwise randomized comparisons of different chemotherapy regimens yield null results then this supports the hypothesis that none of them is effective.

The starting point of the present assessment was recent surveys of the state of the art of clinical oncology, especially those published by the EORTC on randomized trials in cancer. I attempted to gain a comprehensive and up-to-date view of relevant studies yielding direct or indirect evidence. Apart from searches into medical litera-

ture data banks and the inspection of recent proceedings of congresses, this included a personal enquiry addressed to over 350 oncologists and oncological research units all over the world. The aim of the inquiry was two-fold: first, to ask for information on research that was unpublished or unknown to me and, second, to obtain an idea of the rationale and justification of cancer chemotherapy, particularly put forward by those oncologists who were unable or unwilling to quote direct evidence for beneficial effects.

Direct and indirect evidence

Table Ia/b gives a summary of direct and indirect evidence regarding prolongation of survival through cytotoxic therapy in some major epithelial tumors. Note that the symbols + or (+) merely state the existence of evidence. They do not imply that cytotoxic therapy generally prolongs the expectation of survival, but only that this holds true for at least one regimen. Similarly, the negative signs only extend to the regimens that have been investigated, so far.

Table Ia. Direct evidence from randomized studies on the question of whether palliative chemotherapy prolongs survival.

Site	*Type of study*		
	Chemotherapy + X vs X alone (X = any treatment)	*Immediate vs deferred therapy*	*Dose-effect-studies*
Lung, small-cell	+	Ø	–
Lung, non-small cell	(+)	–	Ø
Colon/rectum	Ø	unclear	Ø
Stomach	–	Ø	Ø
Pancreas	–	Ø	Ø
Bladder	Ø	Ø	Ø
Breast	–	(–)	–
Ovary	Ø	Ø	unclear
Cervix Uteri	Ø	Ø	–
Endometrium	Ø	Ø	Ø

Ø: There is no evidence of this type; + or –: The evidence is definitely positive (negative, response); (+) or (–): Unclear evidence; on the whole rather positive (negative, respectively). In case of (+): the effect is, if any, small.

Table Ib. Indirect evidence on the question of whether palliative chemotherapy prolongs survival.

Site	*Type of study*	
	Randomized comparisons of different regimens	*Non-randomized comparisons of patient cohorts*
Lung, small-cell	+	–
Lung, non-small cell	unclear	–
Colon/Rectum	–	–
Stomach	–	–
Pancreas	–	–
Bladder	–	–
Breast	(–)	–
Ovary	+	–
Cervix uteri	–	–
Endometrium	–	–

For explanatory notes see table Ia.

For the reasons discussed above, evidence from non-randomized studies (mostly evaluations of secular trends in survival rates) is stated only when negative, *ie*, when it suggests that the introduction and development of chemotherapy has not markedly changed the prognosis of cancer patients.

Even more surprising than the large number of negative signs is the high percentage of zeros. This means that, to-date, the corresponding question has not even been subjected to serious investigation. For a detailed discussion with a substantiation of the statements made in table I for various sites, we refer to the underlying report [1]. Here we will briefly comment on the main evidence, with emphasis on the direct one.

In the case of small-cell lung cancer a prolongation of survival by means of chemotherapy (cyclophosphamide, nitrogen mustard, ifosfamide, or ifosfamide + CCNU) has been established in two randomized trials *versus* no-treatment controls [48, 74]. In addition, a consolidation therapy for responders seems to have a positive effect on survival [36, 65]. Finally, there is considerable and unanimous evidence (see *eg* the eight randomized studies compiled by Malik [84]) that the combination of chemotherapy with radiation therapy is superior to radiation therapy alone. However, the benefit from chemotherapy is by no means striking: the increase in median duration of survival hardly exceeds three months, so that in every single case the side effects of chemotherapy have to be weighed against its rather short–lived success. Two further caveats should be noted. First, no survival advantage was found in three randomized studies [77, 128, 137] comparing chemotherapy with hemibody irradiation. In fact, Laing *et al* [77] even found that for patients having mostly tumors restricted to the thorax and neck region, hemibody irradiation resulted in significantly longer survival than combination chemotherapy with nitrogen mustard + vinblastine + procarbazine + prednisolone. Second, there are not any good indications that high-dose therapy is superior to standard-dose therapy [41, 67, 69, 82, 98]. In an interesting study by Harris *et al* [53], no significant survival difference was observed between a mild, oral chemotherapy given at home and an intensive iv in hospital therapy.

For non-small cell lung cancer (NSCLC), a positive effect of different regimens has been noted in at least eight randomized studies *versus* controls receiving no active treatment [20, 25, 46, 48, 107, 108, 113, 138]. However, the differences in median survival times found in these studies were in the order of only a few weeks and hardly exceed the duration of therapy itself. Moreover, several studies [32, 76, 78] suggest that it may be advantageous to defer treatment in patients without severe symptoms.

Indirect evidence of positive effects of chemotherapy in NSCLC is not more conclusive than direct evidence. While the addition of cisplatinum to standard regimens gave a slight survival improvement in two small studies [38, 45], no advantage was seen in other trials [7, 9]. In addition, in the secular development of survival rates, a distinct improvement over the past 20 years is not perceivable for the entirety of patients [8], let alone for patients in advanced stages who invariably have an extremely poor prognosis with 5-year survival rates of about 2% [122].

In colorectal cancer, even with the most active regimens, complete remissions are still an exception. No randomized trials including no-treatment or low-treatment controls seem to have been published. The only studies providing direct evidence are those by Hine and Dykes [59] and The Nordic Gastrointestinal Tumor Adjuvant Therapy Group [123] comparing immediate therapy (5-Fu + CCNU, sequential methotrexate + 5-Fu + folinic acid, respectively) *versus* a deferred cytotoxic therapy given only when required by the symptoms. (In the study by Hine and Dykes the onset of the treatment was defined not by the detection of metastasis but by the observation of a significant increase in serum CEA). The results of these studies are conflicting. While Hine and Dykes obtained almost identical survival curves, the Swedish Study Group found a significant survival advantage for immediate therapy, the median difference being 5 months. Note, however, that 20 months after randomization, the survival rates in the two patient groups dropped to an identical level. There is not any good indirect evidence of beneficial effects of chemotherapy either. No clear survival difference has been found in randomized studies of various regimens nor is there any positive trend in survival rates with patients with metastasized colorectal cancer [97, 122]. Note that a retrospective study comparing patients receiving 5-Fu with a low-treatment group of comparable structure yielded very similar survival curves [91].

For advanced gastric cancer, only three randomized studies seem to have been published that directly address the problem of whether

chemotherapy extends survival. Essentially, the results of these studies are negative. In an early small study, Moertel *et al* [90] compared the combination of radiation therapy with 5-Fu with radiation therapy alone. There was significant survival advantage for the combination, possibly due to an enhancement of the effects of radiotherapy, but the difference in median survival was less than three months. In a double-blind controlled trial, Kingston *et al* [73] evaluated the efficacy of 5-Fu + MeCCNU compared with placebo in 193 patients with unresectable gastric carcinoma. The groups were well balanced with respect to age, length of history, and performance status. The survival curves were very similar. Dent *et al* [27] randomly assigned 67 patients with stage T4 or M1 to one of three groups: i) a no-treatment control group, ii) radiation therapy +5-Fu, and iii) iv chemotherapy with thiotepa. Survival of patients was the same in all arms of the trial. None of the numerous randomized trials of quite different chemotherapy regimens demonstrated a marked therapeutic difference [60, 85]. While the response rates achieved with monotherapy are typically about 20% or less, up to 50% response can be achieved by combination therapy (*eg*, FAM); however, in most cases, the remission is only partial. There is no evidence that combination therapy is superior to single-agent therapy regarding length of survival.

As for pancreatic cancer, the influence of chemotherapy on survival has been directly assessed in three randomized trials, namely the studies by Mallinson *et al* [87], Frey *et al* [44], and Schnitzler *et al* [111] comparing combination chemotherapy with a no-treatment arm. The results of these trials are unclear. The study by Mallinson *et al* includes 40 patients, 21 of whom were treated with CMFV. Only 15 patients, however, presented with manifest dissemination of the tumor, and in 14 cases histological confirmation was lacking. The chemotherapy group showed significantly longer survival than the control group. In contrast to this result, the more sizeable study of Frey *et al* in 152 male patients with nonresectable, histologically confirmed carcinoma was completely negative. The group receiving cytotoxic treatment (5-Fu + CCNU) had an even shorter median survival (3.0 months) than the control group (3.9 months). A negative result with multiple crossings of the survival curves was also obtained in the study by Schnitzler *et al* [111] using 5-Fu + ADM + BCNU. Again, this study is of limited value, since it contained only 30 evaluable patients (13 treated, 17 controls). The indirect evidence also produces a negative picture. Never have there been any observations of marked (let alone consistent) differences among chemotherapy regimens when compared in randomized trials. This is particularly true for comparisons of single-agent therapy with combination therapy. Since survival rates are still extremely poor, even in patients without manifest distant metastases, no substantial progress can have been made in the past.

Of particular interest is the case of breast cancer since among all cancer sites it is the one to which falls the greatest share of chemotherapy. Modern therapy using various combinations of cytotoxic drugs, like CMF, CAF, or VAC, achieves response rates of 40-80%, yet the proportion of complete responders is almost always lower than 20%.

There is no direct evidence that chemotherapy prolongs survival of breast cancer patients. Both controlled studies using untreated controls and randomized comparisons of immediate *versus* deferred therapy are lacking. There are, however, some investigations approaching the latter comparison, namely, trials of combined endocrine/chemotherapy *versus* either endocrine single-agent therapy or a sequential endocrine-chemotherapy. Unfortunately, the seven studies of endocrine *versus* combined hormone/chemotherapy are very small (see the survey by Macaulay and Smith [83] as well as the publication by Kiang *et al* [72] and they do not yield any clear indications for differences between the treatments. Negative findings also result from the numerous comparisons of sequential *versus* combined applications of endocrine/chemotherapy. Two recent, fairly large, and well documented cross-over studies (Taylor *et al* [120], The Australian and New Zealand Breast Cancer Trials Group [121]) are worth mentioning. In the study by Taylor *et al*, 181 patients aged 65+ years received either initial treatment with Tamoxifen or CMF. On progression they were crossed over to the other treatment. In this study, initial hormonal therapy was not only significantly less toxic but induced a slightly longer survival than CMF, both in ER-positive and ER-negative patients. The three-arm Australia/New Zealand trial compared sequential administration of AC + Tam (starting either with chemo- or hormono therapy) with AC + Tam given simultaneously in 339 post-menopausal patients under 70 years. The survival in all three groups was virtually identical.

There are more than 30 randomized trials in which therapy given to the patient groups consists of the same combinations of cytotoxic drugs and differs only in the intensity of the route and timing of administration (for reviews see [58, 83, 103, 119]). In some of these studies survival has not been analysed and others are too small for any meaningful evaluation. Marked or significant differences favoring the more intensive regime have neither been found for single-agents like 5-Fu or doxorubicin nor for combination chemotherapy. Observe that for the reasons discussed above, the dose-intensity analysis presented by Hryniuk and Bush [63] is of little value and cannot question the results of randomized trials. A comment is warranted on the only two studies that resulted in discernible treatment differences. In the study by Tannock *et al* [119], two different doses of CMF were compared. There was a significant (though small) advantage for the higher dose (median survival = 15.6 *vs* 12.8 months) but this may be due to the fact that there were highly significant differences between the treatment groups with respect to prognostic factors. After adjustment for this imbalance, the survival differences were no longer statistically significant. Carmo-Pereira *et al* [17] compared identical cumulative doses of doxorubicin given in two regimens of different intensity and length. The shorter and more intensive application was found to yield longer survival. Of course, this does not imply that higher single doses are advantageous as such. In this context, a study by Harris *et al* [52] is noteworthy; a slightly better survival was observed for short-term administration of mitoxantrone compared with a continuous administration of identical doses of the same drug. Furthermore, there is no indirect evidence for beneficial effects of chemotherapy on survival. An enormous number of phase-III studies have been conducted comparing a variety of quite different regimens, but never (and this is actually surprising in view of the large amount of material) have there been any findings of a distinct, let alone reproducible, survival advantage (see [54, 57, 83, 103]). In particular, this holds true for the comparisons of combination *versus* single-agent chemotherapy. In one study [15], a significant advantage of CMF over L-Pam was observed but the difference was small (median survival = 12 *vs* 9 months) and the mean DFS in the CMF-group was 3 months longer than in the L-Pam group, thus favoring CMF somewhat with respect to prognosis. Moreover, the difference was confined to patients with poor initial prognostic status, namely those with liver metastases, or non-ambulatory performance status. Ahmann *et al* [2] conducted a meta-analysis of three consecutive randomized studies of combination chemotherapy *versus* single-agent chemotherapy with methyl-CCNU, ifosfamide, or adriamycin (a total of 131 patients). After pooling the single-agent groups, the median survival for the combination was 3.7 months longer, but ifosfamide alone was even superior to the combination. In addition, the difference found in the meta-analysis was not statistically significant.

An additional comment on the subject of breast cancer is called for. It has been claimed that aggressive chemotherapy can prolong survival in certain sub-groups, particularly in patients with a 'high risk', *ie*, a poor prognosis. These assertions are based on sub-group analyses of randomized studies comparing regimens of different aggressiveness [*eg*, 11, 12, 15, 19, 72, 106, 121]. Now, as is well known, analyses of this type tend to produce artefacts [81]. Moreover, an evaluation of the relevant studies shows that the findings are by no means clear and consistent. Thus, in a more recent, extensive well-designed clinical trial comparing endocrine and cytotoxic therapy given sequentially or in combination [121], no subgroup could be identified that profited from the more aggressive strategy.

As for the secular development of survival rates of breast cancer patients, publications are contradictory, the weight of evidence being rather negative (*eg*, [70, 93, 100, 101, 104, 109, 110, 125, 131, 132, 140]). In this regard, Henderson *et al* [57] correctly state: "Most retrospective studies have failed to show that the survival of patients with advanced breast cancer has changed very much over the past 20–30 years".

Summarizing, one still has to agree with Macaulay and Smith [83], who conclude their comprehensive survey of randomized studies in advanced breast cancer with the following remark: "On this basis there trials argue for a conservative approach to the management of this disease. There is no evidence that asymptomatic patients need any form of active treatment."

Ovarian carcinoma is considered to be a tumor that is sensitive to a cytotoxic therapy; most oncologists are convinced that modern regimens, particularly those containing cisplatinum or its analogon carboplatinum, prolong the survival of patients even in advanced stages (FIGO IV or FIGO III with non-completely resectable tumors),

which are the majority of newly diagnosed cases. This opinion is mainly based on historical comparisons and on unclear indirect evidence from randomized studies. Strangely enough, there is hardly any direct evidence. Randomized comparisons with untreated controls or of immediate *versus* postponed therapy are lacking, and today they would probably no longer be accepted since most clinicians consider the use of chemotherapy as unrenouncible. Also, there are no pure dose-effect studies, at least no randomized ones. The dose-intensity analysis published by Levin and Hryniuk [80] is based on a collection of quite incomparable studies and hence lacks any conclusiveness. There is, however, one small study by Wiltshaw *et al* [136] which compares high-dose cisplatinum with low-dose cisplatinum + chlorambucil. The high-dose arm had longer median survival (24 *vs* 14 months); subgroup analysis indicated that the advantage was confined to patients in stage FIGO III with a residual tumor greater than 2 cm. The positive (indirect) evidence for ovarian cancer noted in table Ib comes from 13 randomized studies comparing cis-platinum-containing combination chemotherapy with non-cis-platinum- containing chemotherapy [5, 16, 23, 26, 35, 50, 79, 96, 99, 116, 118, 130, 134]. Though the results are not quite clear and consistent, they tend to give support to the conjectured positive effect of cis-platinum (or its less toxic analogue carboplatinum) for patients in stage FIGO III. There is no indication, however, that this also holds true in stage IV which comprises virtually no 5-year-survivors [75, 136]. And, contrary to the opinion of some oncologists, it is doubtful whether the success in stage III is a durable one justifying a long-term administration of an aggressive therapy. Moreover, it is doubtful if the immediate use of cisplatinum offers an advantage over a sequential strategy starting with a less toxic regimen. Thus, in a large trial comparing sequential chlorambucil + cisplatinum (the latter given in the case of tumor progression) *versus* combined chlorambucil + cisplatinum, the survival in the two groups was practically identical [50].

The association between response and survival

The induction of a remission, *ie* a measurable decrease of the tumour mass, is the primary goal of palliative chemotherapy. Most clinicians judge the "activity" of the therapy by the response rate. Complete as well as partial responders will often not only experience an alleviation of symptoms but, as clinical trials almost unanimously show, they can expect to survive longer than non-responders [117]. This observation leads a great number of oncologists to the conclusion that a response to chemotherapy prolongs the survival time of the patient. In fact, this reasoning seems, at first glance, so obvious and logical that its popularity is hardly surprising. The structure of the argument and of its implications deserves a close analysis. First note that the conclusion is neither logically true nor evident from the facts. It would be a logical implication only if patients responding to therapy survived longer than they would without the treatment, a fact which cannot be deduced from their advantage over non-responders. At least three different explanations can be given for the phenomenon, none of them implying beneficial therapeutic effects. (They are perhaps the reason why differences in survival time between responders and non-responders are no longer accepted by the FDA as evidence for effective treatment, [68]).

i) Time-to-response bias; ii) Selective bias; iii) Overtreatment of non-responders.

Time-to-response-bias is bias due to the definitions; on average, responders should survive slightly longer than non-responders simply because they must live a minimum interval after the onset of therapy in order to be classifiable as responders. Selection bias arises if responders form a subgroup of patients with a favourable prognosis who would have lived longer than non-responders whether they had received the treatment or not. This hypothesis, which is perhaps the most frequent objection to the alleged benefit of therapy to responders, cannot be tested directly, but there are other ways of corroborating it (see below). As for the third explanation, it is fairly obvious that a toxic treatment can be harmful to those patients whose disease does not respond to it. This applies particularly to progressive cases whose state of health often deteriorates rapidly. In this context, another aspect is worth mentioning. Let us assume that responders do benefit from their therapy in expected survival. Many oncologists emphasize that this holds true at least for complete responders. Even then, this effect cannot be used as a self-evident argument in favour of the therapy unless it can be shown that there is a benefit for the entire patient group as otherwise the gain seen in responders must have been compensated for by the loss suffered by non-

responders. In these circumstances the treatment raises a considerable ethical problem.

In what follows we want to analyse more closely the hypothesis of an improvement of prognosis in responders, brought about by the therapy. If this hypothesis were true, one would expect and postulate that of two therapies yielding different response rates, the one giving the higher rate should be superior as to survival; this difference must be demonstrable in randomized studies and it must be reproducible. The requirement of reproducibility is important since in a single study the results might be attributed to prognostic factors. If produced repeatedly, however, this argument would fail because it would be inexplicable that the prognostically superior group of patients should always lie in the same arm of the trial.

Let us have a look at the data in the light of these arguments. It is well known from clinical trials, though somewhat enigmatic to the non-oncologist, that, while the response rates of tumours show extreme variations with different chemotherapies, this is not reflected in clear differences in the corresponding survival curves. One has to distinguish between the variability of rates obtained when compiling published trials, and the differences between response rates of two or more regimens compared in the same randomized trial. The former can be explained quite naturally by diverging study designs. Note that the response rate found in a patient sample is known to depend on a number of factors such as patient characteristics, treatment, method of data collection, or statistical variability [33, 34, 71, 117, 126, 133]. Nonetheless, the extent of the ranges of rates found in clinical studies is quite surprising. Thus, a recent survey of randomized studies of combination chemotherapy in advanced breast cancer [83] lists 75 groups (arms of different trials) including more than 40 patients each; the achieved response rate ranges from 25–76%. Similar ranges are found in colorectal and stomach cancer. Still more intriguing are the striking differences in response rates found between the arms of the same randomized trials which are not reflected in differences in survival curves. Not infrequently, even the arms showing lower response rates do better in their survival.

The lack of any apparent relationship between response and survival is by no means biologically implausible. The reduction of a large tumour mass by 50% may simply by insufficient for a significant change in the course of an advanced disease [37]. It is likely that tumour size is less important for prognosis than the distribution of tumour mass, *ie* the site of metastasis. Also, there are empirical findings indicating an enhancement of malignancy as a result of chemotherapy [88].

Does chemotherapy improve the quality of life?

Many oncologists admit the lack of evidence for positive effects of chemotherapy on the duration of survival in advanced solid cancer; yet, they point out that this is not the primary goal of treatment, but that chemotherapy is aimed rather at improving the quality of life (QL) of the patients. This point of view is entirely legitimate. Moreover, if toxic cancer treatment cannot prolong survival, then the therapist has the duty to furnish proof that it improves QL. New QL is a complex and somewhat hazy notion. It includes tumour-related symptoms as well as the various toxic effects of therapy, and numerous further parameters of subjective well-being such as appetite, capability of continuing normal activities, and the degree of anxiety or depression.

The measurement of QL raises many methodological problems concerning the scale, validity, and reliability of the measurement. Several different instruments have been proposed and used in clinical trials but, as yet, no consensus has been reached on the selection of relevant variables, the method and timing of data collection, the weighting and combination of the parameters [30, 47, 89, 129]. In principle, adequate proof of improvement of QL due to therapy can be obtained in randomized studies only (unless the definition of QL exhausts itself in a description of toxicity of therapy). Phase-II studies monitoring the parameters of QL are not very convincing because in these studies therapeutic effects cannot be separated from the factor "intensity of medical care".

Palliation in the narrower sense, namely the relief of tumour-related complaints, is certainly one aspect of QL which is easier to demonstrate. Often the effects are so evident that there is no need for a verification by clinical trials. Indeed, many oncologists justify their use of chemotherapy with reference to palliation. In clinical practice, however, this justification applies only to a fraction of the patients treated, *eg*, according to Drings [31], to patients suffering from severe pain, pleural or other effusions or paraneoplastic syndromes. A look at the guidelines for standardized tumour therapy [103, 115] shows that at least for some tumour sites an application of

chemotherapy is recommended independently of the patients' symptoms.

There are at least three reasons why in reality cytotoxic treatment is not restricted to symptomatic patients. First, a large number of oncologists are convinced of the therapeutic effects. They justify the early use of chemotherapy by virtue of its apparent success. Second, the generally accepted demand to treat patients if possible within the scope of clinical studies leads to the result that many patients are treated according to uniform study protocols rather than to individual plans suiting their symptoms and needs. Third, the patients' request for treatment may play a role. Desperate patients will urge the doctor to become active and willingly accept considerable side-effects of treatment, if only to escape the passiveness of waiting (see the description of the problem by Nagel [95]). It is doubtful, however, whether this natural request can justify a toxic treatment which does not prolong the expected duration of survival and which is applied without an immediate need for palliation.

Also, the aim of palliation of symptoms by chemotherapy conflicts with the maxim followed by some oncologists that the more aggressive cytotoxic therapy is the more promising it is.

Let us return to the more general concept of QL. It has been noted in several clinical studies [4, 10, 42, 105, 124] that the responders to chemotherapy may benefit from the treatment as to their QL. The benefit can be threefold: First, as already mentioned, the tumour remission can lead to relief from pain. Second, after the induction of a partial or complete remission, the aggressive therapy is often stopped so that the responders are spared toxic side-effects. Finally, response has positive effects on the patients' psyche. An improvement in mood as a result of chemotherapy can, despite the side-effects, be induced even if the patient is symptom-free at the beginning of the treatment, for the response to therapy and the hope brought about by this response is, independent of objective justification for it, an important component of QL [55] and thus an essential part of medical care.

It would, however, be a serious, though common error, to assume that the gain in QL seen in responders is an indisputable argument in favour of therapy. The (statistical) proof that treatment leads to an improvement in QL must be furnished for the entirety of the treated patients. Since responders cannot be determined in advance, their possible benefit from chemotherapy must be balanced against the harm done to the other patients.

To date there have been no randomized studies yielding clear evidence for an improvement of QL by means of chemotherapy. This is hardly surprising because the evidence must satisfy the same high methodological standard as in the case of survival. In other words, the same studies which, by their design, are suitable for showing a survival benefit due to a therapy, are also suited for providing evidence of an improvement of QL by treatment. In the case of QL one can expect, *a priori*, to find even less evidence because the measurement of subjective well-being has rarely been part of the clinical trials. Clearly, studies in which the investigation of QL is, as is usual, restricted to the treatment-related toxicity cannot yield evidence of an improvement of QL.

To the author's knowledge, the only studies attempting to furnish direct evidence are the three trials mentioned above comparing immediate chemotherapy with deferred therapy in non-small cell lung cancer. In these studies, QL in the no immediate treatment group was at least as good as in the immediate treatment group. Indirect evidence has been provided in the studies of Baum *et al* [4] and Coates *et al* [22] for patients with breast cancer. While the results of these investigations give some indication that QL may be improved by chemotherapy, the study designs have severe methodological flaws which, moreover, are of a kind that might have produced the finding as an artefact. Thus, in the study by Coates *et al*, patient groups differed with respect to the frequency of the visits to the doctor and the hospital. Also, time-dependence of well-being was not adequately accounted for. (See [1] for a more detailed discussion of these studies). It is worth mentioning that in a recent matched-pair study comparing chemotherapy with an unconventional cancer treatment it was found that the decrease of QL over time was very similar in the two groups [18].

Today, many responsible oncologists are aware of the fact that strong evidence, both for a prolongation of survival and for an improvement of QL by chemotherapy in advanced solid cancer is lacking, and they draw practical consequences from it. Thus, the "Consensus-Development-Conference" [24] gives the following recommendation for the use of chemotherapy in metastasized breast cancer: "For most patients with metastasized disease one should start with endocrine therapy as a first-line treatment".

It should arouse concern, however, that according to opinion polls, many oncologists would decline to accept cytotoxic therapy in their own case [3, 51, 86, 92]. Also, the observation made by Holli *et al* [61] on 252 patients with advanced breast cancer that the "risk" of receiving cytotoxic therapy was three times as high in the terminal stage as in the remainder of the patients, does not point to a use of therapy which is particularly geared to patients' well-being.

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