problems associated with large clinical trials. As purchasers and providers become more aware of the need for economic analysis to inform decision-making, they will also need the relevant data quite rapidly if it is to be of immediate use and studies such as this one show that this is indeed possible in some contexts. However, such an approach would not always be appropriate and large scale, longer term clinical and economic evaluations will be needed in many cases if robust results are to be obtained.

In conclusion, this study provides insights for decision makers and can guide the efficient use of resources devoted to health illustrating how a narrow focus on one aspect of costs alone can provide misleading and inappropriate conclusions. It also highlights some of the methodological issues involved in the economic analysis of cancer treatments. It shows how such analyses can sometimes be undertaken on a small scale, and in a simple manner, yet still provide useful information and whilst the small numbers and short time scale remind us to view it perhaps as a pilot study rather than a definitive trial, it will clearly be useful to those involved in the provision of care for patients undergoing chemotherapy for cancer.

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Workshop on Suramin with Emphasis on Prostate Cancer: Re-evaluation of Response Criteria

Ruud E.N. van Rijswijk, Esteban Cvitkovic, John Wagstaff and Charles E. Myers, on behalf of the participants of the meeting*

DURING THE seventh NCI/EORTC symposium† a workshop took place with the aim of discussing the present status of suramin in the treatment of cancer. The meeting was intended to have a broader perspective, however, as suramin analogues are oncoming. A common language regarding the response criteria to be of use in clinical trials with these novel agents was therefore felt to be of special importance. Two main topics were listed on the agenda. Firstly, to critically reconsider response criteria of trials in prostate cancer involving growth factor antagonists. Secondly, to evaluate the anticancer activity of suramin.

The initiative for this meeting arose from the opinion, expressed especially by European investigators, that the toxicity of suramin might offset its use as an anticancer agent. In particular the severe motor neuropathy observed in a number of patients treated with the drug had led to this concern. During the past year it has, however, become evident that the schedules of administration of suramin used in early studies were not optimal. It is now apparent that the peculiar pharmacokinetics (mean $T_{\frac{1}{2}}$-α value of 14 h and mean $T_{\frac{1}{2}}$-β value of 55 days) of suramin require an individualised dosing schedule in order to keep peak and trough concentrations within suramin's narrow therapeutic window. The minimal concentration required to obtain an antitumour effect has not been clearly defined. Based on IC_{50} values of various prostate cancer cell lines exposed to suramin, Myers felt that a trough concentration of at least

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150 μg/ml might be sufficient to obtain responses in prostate cancer patients. The peak level should remain below 300 μg/ml, as higher concentrations have been associated with the occurrence of motor neuropathy [1].

At plasma concentrations around 150 μg/ml suramin binding to albumin is as high as 99.7%, and the fraction of free suramin conversely is low under these conditions. The binding of suramin to plasma components at higher plasma concentrations is however not linear and, consequently, high concentrations of free suramin may occur immediately following bolus administration when peak total suramin concentrations may exceed 300 μg/ml. Although the antitumour activity of suramin appears to be mediated by its unbound fraction, the contribution of these high free suramin fractions, which occur in the intravascular compartment only for short periods of time, to the cytostatic effect of the drug is probably very limited. *In vitro* studies have shown that a long-term exposure to suramin is necessary in order to obtain maximum inhibition of cell proliferation [2]. High peak concentrations may however be very important mediators of the toxicity of the drug. Studies at the university of Antwerp, measuring total and free suramin concentration, showed that this indeed appeared to be the case [3]. Much of the toxicity of suramin could be explained by these high free suramin concentrations.

Accurate dosing of suramin aimed at preventing potentially toxic plasma concentrations is therefore mandatory. This requires close monitoring of suramin plasma concentrations during treatment and adaptation of the dose to patients' individual pharmacokinetics. In this respect, computer-assisted modelling using Bayesian pharmacokinetics appears a valuable technique for keeping the suramin concentrations within a predefined window [4, 5]. Strict adherence to these guidelines has considerably reduced the severity of the neuropathy [6].

A major topic of the meeting was to reach a consensus in defining response criteria to be used in trials with biological agents and other compounds interfering with autocrine or paracrine stimulated tumour growth. The commonly used WHO criteria to assess tumour response to cytotoxic agents [7] may not be fully appropriate for monitoring tumour response in patients treated with agents interfering with proliferation without being directly cytolytic. In patients treated with these latter agents it has been observed that "stable disease" does not necessarily imply absence of a valuable therapeutic effect. Alfa-interferon treated patients have shown objectively stable lesions that contained an increasing degree of fibrosis which was replacing viable tumour cells [8]. Myers showed that this also holds for patients treated with suramin. One of the prostate cancer patients showed a persisting lesion which turned out to be an area of necrosis upon removal of the tumour. Theoretically, such residual lesions might also be composed of differentiating cells, analogous to those observed in malignant teratoma patients treated with cytotoxic agents, or cells which have been induced to undergo apoptosis, a process which may take some time to occur. It was therefore agreed that persisting lesions in patients who otherwise show remission of their disease as suggested by declining tumour markers should be biopsied whenever feasible.

One of the diseases in which suramin appears to be most promising is hormone-refractory metastatic prostate carcinoma. Response evaluation in these patients constitutes a special problem. In the majority of patients with metastatic prostate carcinoma the bulk of the disease is localised in the bone. Bone scans are an insensitive means of assessing response, as repair processes and flare phenomena may mimic progressive disease [9]. The majority of prostate cancer patients do not have measurable disease as defined by the usual criteria. This makes documentation of response by conventional WHO response criteria impossible. For this reason, criteria specifically tailored to the documentation of response in prostate cancer patients have been developed [10–12]. Apart from objective response criteria, subjective elements and changes in biochemical parameters have commonly been added to these response criteria in order to accommodate for the evaluation of non-measurable disease. Until recently, it has been controversial as to whether biochemical changes are a meaningful parameter of response to therapy. To circumvent this problem, many phase II studies in prostate cancer have only included patients with conventional measurable disease. These patients are not representative of the average prostate cancer patient with bone metastases as the predominant site of disease, which suggests that novel markers of objective tumour response are needed.

Prostate specific antigen (PSA) might be an important candidate which fulfils these requirements. PSA is a glycoprotein of 33 000 Da with an estimated serum half life of 2 days. In patients with newly diagnosed localised prostate cancer who have undergone radical prostatectomy, PSA levels always became normal in patients rendered tumour-free by the surgery, whereas persistence of elevated PSA levels pointed to occult metastatic disease. The presenting serum concentration of PSA in these patients also corresponded to the tumour volume removed. In patients with metastatic disease being treated with an initial endocrine therapy, a fall in serum PSA levels is a predictor of response (reviewed in Ref. 13). Evidence was supplied that in patients treated with suramin serial measurements of PSA might also be of value in predicting response to therapy [6]. Marked decreases in serum PSA concentrations were observed in responding patients with bone-only disease and also in patients with soft tissue disease. In the latter group of patients, objective tumour response correlated with a decrease in serum PSA $> 80\%$ in the majority of them. More importantly, however, marked decreases in serum PSA corresponded with increased survival times. The cut-off point between long-term survivors and patients showing no improvement in survival appeared to be a 75% decrease in PSA or more.

Several other groups have confirmed the favourable response rate of suramin in hormone-refractory prostate cancer, initially reported by Myers *et al.* [6]. 8 of 21 evaluable patients with measurable disease reponded to suramin, as reported by Salmon, and 88% of these patients had a reduction in PSA serum concentrations of $> 80\%$. The Amsterdam group obtained a 20% response rate in 30 patients who started suramin therapy, as defined by a $> 90\%$ decrease in PSA. Patients who had clinically progressive disease, however, did not show the expected logarithmic increase in serum PSA concentrations after treatment with suramin. Consequently, a stable PSA level during suramin therapy does not exclude progressive disease.

The general conclusion was therefore reached that in patients with hormone-refractory prostate carcinoma a decrease in PSA of $> 80\%$ from pretreatment values for a duration of 2 months or more indicates response, unless clinical evidence suggests the reverse. In patients who have a normalisation of PSA, but still show residual soft-tissue disease, these tumours should be biopsied in order to assess response. Ultimate endpoints should be rebiopsy and survival times. The apparent plasma $T_{\frac{1}{2}}$ of PSA as a predictor of the quality of the response should be evaluated prospectively. According to Myers, a PSA marker reduction of $> 80\%$ within weeks after the commencement of suramin ther-

apy usually heralds a meaningful tumour response, even in the absence of complete normalisation of the marker level. Still unanswered is the question of how long suramin has to be continued, once disease stabilisation or response has been obtained, and what would be the optimal target plasma concentration for maintenance treatment in these circumstances. Efforts should be undertaken at defining the subgroup of prostate cancer patients who are most likely to respond to suramin, based either on pretreatment characteristics or biochemical changes which occur early after the initiation of therapy.

A number of phase II trials exploring suramin in other tumour types are ongoing. These include renal cell carcinoma, adrenal cortical carcinoma, non-small cell lung cancer, melanoma, ovarian carcinoma and malignant glioma. Salmon reported a 15% response rate in ovarian carcinoma patients. The activity of suramin in malignant melanoma, however, appears to be modest. Several *in vitro* studies have indicated synergism between suramin and other biological response modifiers or cytotoxic drugs [14, 15]. Future developments will include the combination of suramin with these agents.

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Axillary Lymph Node Metastasis in Breast Cancer: Prognostic Indicator or Lead-time Bias?

INTRODUCTION

AXILLARY LYMPH NODE metastasis is the strongest predictor of disease-free and overall survival in breast cancer and is the single most important prognostic factor used in the clinical management of the disease [1]. The prognostic influence of axillary lymph node metastasis is mediated through two mechanisms: the relative risk of relapse and death (hazard rate) [1–3] and the relative length of time to relapse and death (delay) [4–6]. These two prognostic end-points have a strictly arithmetic relationship with the number of involved lymph nodes; the hazard rate increases and the disease-free period decreases with progressively increasing involvement of the axilla [1–6].

An important issue relating to the natural history of breast cancer has so far not been settled. This is whether the relatively poor prognosis of patients with breast cancer that has spread to the axillary lymph nodes is due to an increased biological aggressiveness and/or metastatic potential of the tumour or a greater chronological age at diagnosis, or a combination of these possibilities. To address this issue, a meta-analysis of all published reports on correlations between various prognostic factors in breast cancer has recently been performed [7]. The conclusion from this meta-analysis, together with other evidence [4–6, 8–15], strongly suggest that axillary lymph node metastasis (and tumour size) has little to do with the biological behaviour of breast cancer but is a reflection of the relative chronological distance between inception and diagnosis of breast cancer. Viewed from this standpoint, the prognostic influence of axillary lymph node metastasis, both in terms of hazard rate and delay, can be explained entirely on the basis of a lead-time effect.

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BIOLOGY OR CHRONOLOGY?

Post-relapse survival

While it is agreed that the presence (and extent) of axillary node metastasis is the best predictor of disease-free and overall survival in breast cancer, one aspect of the prognostic influence