in dose escalated form by use of growth factor support—and a current study by this group aims to assess the potential, additional use of peripheral stem cell transplantation.

It seems likely that a proportion of patients with poor prognosis teratoma will remain incurable because of the catastrophic nature of their presentation [22,23]. However, for the remainder, there must be hope that results can be improved. It is becoming increasingly difficult to conduct pilot studies of new treatment approaches in this rare population—and these can only be tested by comparatively large studies likely to require international cooperation. A further difficulty is the toxicity and financial cost of many newer treatments.

An international collaborative effort is currently underway to define agreed, adverse prognostic factors. Similar cooperation is required in the future if we are to test new treatment approaches in randomised trials in these rare patient subgroups. Wherever possible, these patients should be included in clinical trials, or referred to centres participating in such studies. It seems likely that cure rates will improve, but progress may well be slow.

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Eur J Cancer, Vol. 29A, No. 16, pp. 2218–2220, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

To Screen or Not to Screen for Cervical Cancer

Matti Hakama

SCREENING FOR cervical cancer may succeed or fail for a number of disparate reasons. On the one hand, it may fail for reasons associated with the natural history of the disease; a screening test should be able to identify a preclinical phase of the disease, at which treatment is more efficacious than at later clinical stages. On the other hand, it may fail because of medico-socio reasons, including errors by those providing, planning or executing medical services, or by those receiving such services.

In any successful screening programme (i.e. a programme which results in a reduction of invasive cancer or death from cervical cancer), both the natural history (biology) of cervical cancer and the organisation of screening medical services must fulfil the general prerequisites for a successful screening. The programme works as well as its weakest link. Thus, there are

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Revised 14 June 1993; accepted 29 June 1993.

poor and good quality screening programmes, and there are women who respond to an invitation for screening and those who do not. Some programmes will have failed for a mixture of these reasons.

In the absence of optimal design—randomised preventive trials—it is difficult to prove that all programmes have not failed, i.e. that the failure was not a general one. Therefore, screening for cervical cancer can be considered from several points of view (pp. 2320–2325). The purpose of this communication is to demonstrate that some programmes work. My example is from Finland, supplemented with Nordic and other data.

In Finland, the cervical cancer screening programme is a specifically organised Public Health policy. Every woman in Finland, aged 30–55, receives a personal invitation at regular intervals (every 5 years) to attend. In the invitation letter she is given an appointment place and time. The result of the PAP test is also given by mail, independent of whether normal, suspicious or malignant. Approximately 400 000 women with 1 400 000 woman-years with information on the actual (participants) or potential (non-respondents) first screening were followed and analysed by a cohort design [1]. Among these women were the first ones, under the national policy, to reach the first rescreening after the 5-year interval. The protective effect, in terms of reduction in the incidence of invasive disease among the responders, was about 80%. It could be argued that the responders were a selected group of the target population. Usually, in a spontaneous screening programme, the target population is strictly speaking unknown or undefined. In the organised Finnish system, the target population was identified from the national population registry and received a written invitation. The risk of cervical cancer among the total target population may be unchanged, depending on the rate of attendance and the risk of cancer among non-responders. The incidence of invasive cervical cancer among the target population in our study, responders and non-responders combined, was 40% of that among the controls, showing, therefore, a 60% protective effect due to screening.

While an effect of the selection described above on the protective effect could be ruled out, there still was the problem of unbiased choice of controls for the target population. We used the total Finnish female population as controls and used the incidence for the whole of Finland shortly before the start of the national programme as the expected risk. It can be argued that there was a decreasing trend in the overall incidence already taking place before the start of the programme, and that the estimate of the protective effect was due to biased expected rates. The lag between the control rates and screening rates was short and, if anything, there was an increasing trend in the overall incidence of cervical cancer in all the Nordic countries, including Finland, before the start of screening [2]. Such a trend was recently confirmed in Estonia where no screening has been practised [3]. With the liberalisations of sexual mores this is what one would expect.

Therefore, the most convincing evidence does not stem from (acceptably unreliable) time trend and case–control analyses, but from cohort studies with the target population identified. However, time trend analyses of the incidence and mortality rates in the Nordic countries [2–4, 5] and otherwise [6–8] confirmed the Finnish cohort study results, and are preferable to the cohort study, probably because of their illustrativeness and simplicity.

Some of the screening programmes work. The difference in effective and ineffective programmes is not related to the natural history of the disease but rather to the organisation of the programme. The elements of the Finnish programme were similar to those listed, e.g. in a UICC report [9]. In the present issue of the *European Journal of Cancer* there are the Europe Against Cancer Guidelines (pp. 2329–2330), which consist of a more elaborate list than the early ones. Such guidelines indicate how to organise a screening programme, although it seems that sometimes these are difficult to apply. Many of the goals in quality of a screening programme (i.e. activities of the health services) can be obtained by organisation, education, monitoring and evaluation. In contrast, it seems that the simple means needed to educate women to attend remain rather ineffective. Therefore, the attitude of the society needs to be changed to make participation easier and more attractive, and so not only the compliance of individual women but also the compliance of society and health services should be targetted.

There is good empirical evidence on the distribution of the length of the preclinical, detectable phase of cervical cancer, on the risk at different ages and on the effectiveness of screening by age. The most well-known source of information is the large scale international study [10] coordinated by Day while he was at the International Agency for Research on Cancer. Therefore, the effectiveness can be estimated without assumptions or mathematical modelling, and the variation in recommendations and guidelines on the ages and frequency of screening is not due to incompleteness or biased data, but rather because of differences in accepting and selecting the evidence, difference in opinion, or difference in values.

While the effectiveness can be relatively reliably evaluated, some of the adverse effects are more problematic. First, there are lesions fulfilling histological criteria of malignancy but without the malignant potential to kill the woman during her lifetime, resulting in overdiagnosis and sometimes overtreatment. The frequency of such lesions depends on the transition probabilities from dysplasia to carcinoma *in situ*, and from carcinoma *in situ* to invasive disease. Estimating the probabilities by follow-up of small groups of patients will inevitably lead to bias, e.g. because the diagnostic manouvre may destroy the lesion. It is more reliable to estimate the life time risks of such lesions by epidemiological means on the basis of screening materials, and to compare the life time risks of preinvasive lesions to that of invasive cancer. More importantly, however, the transition probabilities are a reflection more of the local diagnostic practices than of any general biological phenomena. In Finland, the diagnostic standard adopted results in CIN III lesions, of which one in three would have progressed into invasive disease if left untreated [11]. In Sweden, the transition probability is substantially smaller, and in several years the annual number of carcinoma *in situ* lesions was about five times the number of invasive cancers before screening [11].

Second, the quality of life effects are poorly known and research is rare. Often the women who attend screening do so to be reassured [12] rather than to reduce the risk of death, i.e. the women attend because of quality of life reasons. Important research on anxiety caused by screening invitations, false or correct positive tests and other quality of life aspects have been and are currently being conducted, especially in the U.K. [13, 14].

To screen or not to screen does not depend on poor information about biological effects or on organisational aspects. The decision depends on balancing the effects on the length of life (which is well known and easy to establish), on the quality of life (which is poorly known and difficult to measure), and on the cost (which

give greater value or weight to the length of life, women value the quality of life, while those responsible for administration are cost conscious. Therefore, the decision to establish and continue screening programmes depends not only on the factual evidence available, but also on whose values of the benefits, harm and costs prevail.

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Eur J Cancer, Vol. 29A, No. 16, pp. 2220–2222, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

Papers

Infections in Patients Treated with High-dose Chemotherapy for Germ Cell Tumours

Gedske Daugaard, Henrik Nielsen, Brita Bruun, Flemming Hansen, Poul Geertsen and Henrik Schønheyder

25 patients with disseminated germ cell tumours were treated with high-dose cisplatin and etoposide (40 mg/m² and 200 mg/m² daily × five, respectively) leading to severe myelosuppression. A comprehensive study was undertaken in order to identify and describe the bacterial, viral and fungal infections in this group of patients. Fever (> 38.5°C) and leucopenia (white blood cell count < 1.0 × 10⁹/l) were observed in 61 of 90 treatment cycles (68%). A microbiological aetiology compatible with the clinical manifestations of infection could be identified in 33 of the 61 febrile episodes (54%). Bacteraemia occurred in 14 episodes in 12 patients. Eight episodes (57%) involved gram-positive aerobic bacteria.
Eur J Cancer, Vol. 29A, No. 16, pp. 2220–2222, 1993.

INTRODUCTION

SINCE 1984 patients with highly disseminated germ cell tumours and large tumour load/high marker levels treated at the Finsen Institute, Copenhagen, have received intensive chemotherapy with high doses of cisplatin and etoposide. A high degree of myelosuppression has been observed with this regimen, and morbidity and mortality due to infections have been a serious problem. A comprehensive study was started in order to elucidate the bacterial, viral and fungal infections in this group of homogeneously-treated patients, including an evaluation of the usefulness of surveillance cultures in this clinical setting.

MATERIALS AND METHODS

Criteria for eligibility for this group of patients with poor prognosis germ cell tumours have been described previously [1].

Treatment consisted of at least three cycles of combination chemotherapy including 40 mg cisplatin/m²/day × five, etoposide (VP-16) 200 mg/m²/day × five and bleomycin 15 mg/m² every week at 3-week intervals. Cisplatin and VP-16 were administered on days 1 to 5 in every cycle.

The study was performed in three parts as outlined in Table 1. Part one started on day one in each cycle, part two, one day after termination of treatment and part three at the time where