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.

1. Hakama M, Rasänen-Virtanen U. Effect of a mass screening program on the risk of cervical cancer. *Am J Epidemiol* 1976, **103**, 512–517.
2. Hakama M. Trends in the incidence of cervical cancer in the Nordic countries. In Magnus K, ed. *Trends in Cancer Incidence: Causes and Practical Implications*. New York, Hemisphere Publishing Corp., 1981, 279–292.
3. Aareleid T, Pukkala E, Thomson H, Hakama M. Cervical cancer incidence and mortality trends in Finland and Estonia: a screened vs. and unscreened population. *Eur J Cancer* 1993, **29A**, 745–749.
4. Läärä E, Day N, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: association with organized screening programmes. *Lancet* 1987, **i**, 1247.
5. Lynge E. Screening for cancer of the cervix uteri. *World J Surg* 1989, **13**, 71.
6. Ebeling K, Nischan P. Screening for lung cancer—results from a case-control study. *Int J Cancer* 1987, **40**, 141–144.
7. Miller AB, Chamberlain J, Day NE, Hakama M, Prorok PC, eds. *Cancer Screening*. International Union Against Cancer. Cambridge, Cambridge University Press, 1991.
8. Parkin DM, Nguyen-Dinh X, Day NE. The impact of screening on the incidence of cervical cancer in England and Wales. *Br J Obstet Gynaecol* 1985, **92**, 150.
9. Hakama M, Miller AB, Day NE, eds. *Screening for Cancer of the Uterine Cervix*. Lyon, IARC Scientific Publications, 1986.
10. IARC Working Group on Evaluation of Cervical Cancer Screening Programmes. Screening for squamous cervical cancer: the duration of low risk after negative result of cervical cytology and its implication for screening policies. *Br Med J* 1986, **293**, 659–664.
11. Sveriges Officiella Statistik, Gynekologisk hälsoundersökning 1967–1973. Statistiska meddelanden HS, 1, 1976.
12. Kauppinen M, Kauraniemi T, Koli T, Voipio N. Response to the written invitation in a gynaecological mass screening by cytology arranged in Helsinki in 1966. *Acta Obstet Gynaecol Scand* 1970, **49** (Suppl. 7), 1–20.
13. Campion MJ, Brown JR, McCance DJ, *et al.* Psychosexual trauma of an abnormal cervical smear. *Br J Obstet Gynaecol* 1988, **95**, 175–181.
14. Posner T, Vessey M. Prevention of cervical cancer. The patient's view. King Edward's Hospital Fund for London. King's Fund Publishing Office, 1988.

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Papers

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

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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.
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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

Table 1. Study design

	Day										
	1	4	6	7	9	10	12	15	16	18	21
Blood sample*	1,3	3		3		3					
Total CMV antibodies	1,3			3	1				1		
CMV IgM antibodies	1,3			3	1				1		
CMV in urine and mouth rinsing water	1,3			3							
HSV antibodies	1				1				1		
Candida and aspergillus antibodies	1,3			3	1				1		
Bacterial and fungal surveillance cultures†			2		2		2	2		2	2
Legionella antibodies	3			3							
Bacterial cultures from throat, urine, stool and other suspected focus	3	3		3		3					

1 = part 1, 2 = part 2, 3 = part 3. *Complete blood count, liver and kidney functions. During leucopenia granulocyte counts were performed [3]. †From alveolar processes, the buccal mucosa, throat and oral lesions if present. CMV, cytomegalovirus; HSV, herpes simplex virus.

fever (temperature > 38.5°C rectally) and leucopenia [white blood cells (WBC) < 1.0×10^9/l] were present. Patients included in part three of the study had an extensive diagnostic evaluation, including a careful history and physical examination, chest X-ray and routine blood chemistry studies, including daily measurements of WBC and platelets, together with the investigations stated in Table 1. At least three blood cultures were obtained by separate venous punctures before initiating antibacterial therapy.

RESULTS

Characteristics of the study population

Twenty-five males were consecutively included in the study.

The median age was 32 years (range 19–43). The 25 patients had a total of 90 treatment cycles. 1 patient died during a febrile episode with pneumococcal septicaemia after the second cycle. No patients were otherwise lost from the study. Central venous catheters were used in all patients during the study period.

Febrile episodes

Fever and leucopenia were observed in 68% of the cycles. The median durations of fever and leucopenia during the first cycle were 5 days (range 2–17) and 6 days (range 1–12), respectively, and 8 days (range 5–16) and 8 days (range 3–16) during the fourth cycle. Of 61 episodes with fever and leucopenia, a microbiological aetiology compatible with the clinical manifestations could be determined in 33 cases (54%) (Table 2). Infection was suspected clinically in 5 cases (8%) without microbiological documentation (2 cases of pneumonia, 2 cases of tonsillitis and 1 case of otitis media). In 3 cases (5%), herpes simplex virus (HSV) infection was a likely explanation of fever.

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Bacterial infections

Bacteraemia occurred in 14 episodes in 12 patients (Table 2). Eight episodes involved gram-positive aerobic bacteria, five episodes involved gram-negative aerobic bacteria (one episode with two gram-negative isolates), while the last episode was caused by an anaerobic bacterium. In eight episodes, bacteraemia was present on the first day of fever before start of antibiotic therapy, while in the remaining six episodes it developed during on-going antibiotic therapy. In three cases of bacteraemia, bacteria identical to the blood isolates were found in surveillance cultures [2] or culture from an infectious focus [1].

Viral infections

8 patients were initially HSV antibody negative and 17 patients were positive. 3 patients became infected with HSV during therapy (culture positive with seroconversion) and 7 previously infected patients had a reactivation of their HSV infection (1 culture positive, 2 culture positive with > 4-fold increase in HSV titre, 4 with > 4-fold increase in HSV titre alone).

Other infections

None of the patients demonstrated symptoms compatible with cytomegalovirus (CMV) infection, *Legionella pneumonia* or fungal infections during therapy.

Oral microflora

The grade of stomatitis increased when the WBC decreased but no differences in the numbers of positive surveillance cultures were observed in patients with grade 1 to 4 stomatitis (WHO classification [2]).

DISCUSSION

The present study confirms that patients with solid tumours treated with intensive chemotherapy have a risk for serious infections comparable to that seen in patients with haematological malignancies. Bacteraemia was diagnosed in 23% of the episodes with leucopenia/fever in the present study. In 54% of the episodes with fever and leucopenia, a microbiological aetiology comparable with clinical manifestations could be estab-

Table 2. Microbiologically results

	Bacteriaemia	Mouth, throat	Skin lesions‡	Urinary tract	Diarrhoea	Other
Staphylococcus aureus	1		2		2	
Coagulase-negative staphylococci	2					
Haemolytic streptocci	2*	1				
Streptoccus mitior	2					
Streptoccus pneumoniae	1	1				
Enterobacter cloacae	2			1		
Pseudomonas aeruginosa	3†		2			
Eschericia coli	1†		1	1		
Klebsiella pneumonia			1			
Different anaerobes			2			
Clostridium inocuum	1					
Clostridium difficle					14	
Herpes simplex		4		1		5§

*Group A and group G. †One infection was polymicrobial: *P. aeruginasa* and *E. coli*. ‡Intravenous catheter infections, abcesses and wounds. §One herpes virus type II infection, 4 patients with > 4-fold increase in HSV titre.

lished. Overall, a likely explanation of fever could be obtained in 67% of the episodes.

A clear association between severe stomatitis and severe granulocytopenia could be observed. But in accordance with other studies [3, 4] surveillance cultures were of limited value as predictors of invasive infection in this group of granulocytopenic patients. In 2 cases (14%), a possible association between oral infection and bacteraemia could be established.

The source of bacteraemia was the central venous catheter in 14% of the cases in the present study. This is comparable to data obtained by others [5].

Forty-three per cent of the positive blood cultures were obtained during antibiotic therapy, and additional blood cultures from patients who did not respond to treatment as expected seemed useful. Whether these additional blood cultures should be taken every day during fever and granulocytopenia remains unclear.

Gram-positive bacteria comprised the most common bacterial isolate in the present study. During the 1980s, these bacteria became increasingly prevalent in granulocytopenic cancer patients who became febrile [4, 6].

Immunocompromised patients are at high risk of developing HSV infections caused by reactivation of the virus. Several studies have illustrated a high incidence of active HSV infection among immuno compromised patients, who have had previous HSV infection [7]. In contrast, true primary infection is unusual. However, in the present study, 38% of the initial HSV-negative patients became infected during treatment compared to 41% of those patients with a previous HSV infection.

In conclusion, patients with solid tumours treated with intensive chemotherapy have a high incidence of episodes with granulocytopenia and fever. These patients need intensive monitoring of possible infectious foci. The use of broad-spectrum antibiotics, directed at the predominant infectious isolates at a given institution, obviate the need for routine surveillance cultures. Repeated blood cultures, even in patients receiving antibiotic therapy, can specifically influence therapy and outcome, and may be justifiable for patients receiving maximum supportive care.

1. Daugaard G, Rørth M. Treatment of poor-risk germ-cell tumors with high-dose cisplatin and etoposide combined with bleomycin. *Ann Oncol* 1992, 3, 277–282.
2. *WHO Handbook for Reporting Results of Cancer Treatment*. WHO publication No. 48. Geneva, WHO, 1979.
3. Daw MA, MacMahon E, Keane CT. Surveillance cultures in neutropenic patients. *J Hosp Infec* 1988, 12, 251–261.
4. Pizzo PA. Evaluation of fever in the patient with cancer. *Eur J Cancer Clin Oncol* 1989, 25, 9–16.
5. Klastersky J. Infections in compromised hosts: considerations and prevention. *Eur J Cancer Clin Oncol* 1989, 25, 53–61.
6. Menichetti F, Favero AD. The role of gram-positive therapy in the neutropenic patient. *J Antimicrobiol Chem* 1991, 27, 51–60.
7. Greenberg MS, Friedman H, Cohen SG, Oh SH, Laster L, Starr S. A comparative study of herpes simplex infections in renal transplant and leukaemic patients. *J Infect Dis* 1987, 156, 280–287.

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