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Phase II Study of Oral Miltefosine in Patients with Squamous Cell Head and Neck Cancer

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MILTEFOSINE (HEXADECYLPHOSPHOCHOLINE) is a synthetic phospholipid derivative with *in vivo* activity against the transplanted KB (head and neck) tumour. Because of its similarity to lecithin, miltefosine is suggested to interfere with cell membrane functions [1, 2] but the exact mode of action is yet to be revealed. In phase I studies with the oral formulation nausea and vomiting were the most prominent side-effects [3]. The recommended dose for phase II studies was a daily dose of 150 mg orally, divided over three daily doses. We have now performed a phase II study with daily oral miltefosine in patients with metastatic head and neck cancer.

Patients were required to have histologically proven progressive squamous cell cancer of the head and neck with at least one measurable lesion, a WHO performance score of ≤ 2, white blood cells (WBC) $\geq 4.0 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, creatinine ≤ 140 μmol/l and serum bilirubin ≤ 30 μmol/l. Pretreatment with one chemotherapy regimen was allowed. Informed consent was obtained according to local rules. During treatment haemoglobin, WBC and platelets were checked weekly, while hepatic and renal function tests were repeated every 4 weeks. Miltefosine (ASTA Medica AG, Frankfurt, Germany) was provided as gelatin capsules containing 50 mg of the drug. The starting dose was 50 mg twice daily taken directly after meals. In the absence of side-effects after 1–2 weeks, the dose was escalated to 50 mg 3 times daily. One further dose escalation was permitted to 50 mg four times a day. In case of nausea and/or vomiting not controllable with standard anti-emetics, the daily dosage was reduced by 50 mg until nausea/vomiting resolved and/or were acceptable to the patient.

Response to treatment was assessed after 8 weeks according to WHO criteria. Toxicity was assessed weekly and graded according to WHO criteria; nausea and vomiting were graded as the worst toxicity observed during a whole week.

19 patients were entered on study. Patients' characteristics are given in Table 1. 3 of the patients were not considered evaluable for response because they died before response assessment, 1 after 3 weeks due to progressive disease and 2 after 2 weeks due to unrelated causes. These patients are considered evaluable for toxicity. 1 patient is also not evaluable for response because she discontinued treatment after 3 days because of grade 3 vomiting; this patient is considered evaluable for this toxicity only. The median treatment duration in all patients was 5 weeks, range 0.5–19 weeks. The ultimate dose given was 200 mg in 2 patients, 150 mg in 10, 100 mg in 6, while the single above-mentioned patient did not tolerate 100 mg. The highest tolerable dose was determined by nausea/vomiting, which occurred in 12 patients (6 grade 1, 5 grade 2, 1 grade 3). Emesis could not be prevented by standard anti-emetics, nor by $5HT_3$-antagonists. The only other side-effect was renal toxicity grade 1 in 2 patients and grade 2 in 1 patient. In the latter patient the reversibility of the renal toxicity after discontinuation of miltefosine was not assessed because the patient died of pneumonia 2 weeks after drug discontinuation. In the other 2 patients renal toxicity was reversible after drug discontinuation. There was no myelotoxicity. 3 of the 15 patients evaluable for response had stable disease, the others had progressive disease.

Table 1. Patients' characteristics

No. of patients entered	19
Age (years)	
Median	62
Range	45–78
Sex (females/males)	3/16
WHO performance score	
Median	1
Range	0–2
Primary tumours	
Hypopharynx	9
Oral cavity	4
Oropharynx	2
Sinus piriformis	2
Larynx	2
Prior surgery	15
Prior radiotherapy	17
No. of patients with only irradiated target lesions	5
Prior chemotherapy	9
Drugs	
Methotrexate	4
Cisplatin	3
5-Fluorouracil	3
10-EdAM	2
Sites of disease	
Regional lymph nodes (RN)	5
Lung	6
Lung + RN	1
Lung + liver	1
Liver	2
Lung + local recurrence + bone	1
RN + local recurrence + bone	1
Skin	2

Phase I studies with miltefosine given orally indicated that the therapeutic range was better with daily oral dosing than with intermittent dosing. Although tolerable for some weeks the nausea/vomiting induced by miltefosine when given daily in divided doses remains a cumbersome side-effect, and it cannot be prevented by anti-emetics. Whether the renal toxicity observed, in part is related to dehydration due to chronic nausea/vomiting remains to be elucidated. Although 5 patients only had target lesions in previous irradiated areas with a low chance of response [4], miltefosine given at this dose and schedule cannot be considered an active drug in metastatic squamous cell cancer of the head and neck.

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Computer Tomography (CT) in the Diagnosis and Staging of Cancer of the Penis

A.G. Maiche

CANCER OF the penis is a rare disease in Finland. Its incidence is 0.5/100 000/male population [1]. At presentation, patients generally complain of a penile mass or ulcerating lesion. Some patients may demonstrate inguinal lymphadenopathy [1, 2]. Tumours of the glans and prepuce may metastasise to the inguinal nodes, but if the infiltration involves the corpus spongiosum or urethra, metastases are often also found in the para-iliac and para-aortic nodes [3, 4]. Lymphography is important in the evaluation of the para-iliac and para-aortic lymph nodes, but its straightforward interpretation is often difficult [5–7]. There are presently no reports available concerning the use of computer tomography (CT) as a method of investigation in cancer of the penis, but there are some reports on CT investigations in benign lesions of the penis [8, 9].

The UICC classification of penile cancer of 1987 [10] is based on the depth of infiltration and other histopathological findings. The T code (classification of the primary tumour) could be established according to these rules only in patients undergoing surgery. In a previous study [7], it was demonstrated that although the majority of patients were operated on, one third of the patients could not be classified in regard to this classification. The main aim of the present study was to establish whether CT could be a valuable method in the classification of cancer of the penis, with regard to the T code.

13 men with histologically confirmed malignant tumour of the penis (9 patients with squamous cell carcinoma originating in the penis, and 4 patients with metastasis in the penis from cancers of other sites) were investigated by CT. Contrast enhancement with iopamidol was used. The findings in CT scans were compared with findings with other methods of examination (Table 1).

Table 1. Findings in 13 patients with cancer of the penis by method of investigation, and investigated area

Method of investigation	No. of abnormal findings by investigation area (%)		
	Penis	Inguinal regions	Pelvic and abdominal regions
Palpation	13/13 (100)	6/13 (46)	—
Computer tomography	8/13 (62)	6/13 (46)	6/13 (46)
Lymphography	—	2/3 (67)	3/3 (100)
Histological findings	13/13 (100)	4/6 (67)	—

All primary tumours were palpable. Eight of the nine primary tumours were larger than 2 cm. All four metastases involving the penis were located in the shaft. Eight tumours involving the penis were visible in CT pictures. Four tumours larger than 1 cm with exophytic growth were well detected by CT. All four palpable metastatic tumours in the penis were demonstrated by CT. Small superficial penile tumours found in palpation were missed by CT (Table 1).

Valuable methods of investigation are indispensable in the staging of penile cancer and for rational treatment planning. Actually, there is no reliable physical method of investigation which can demonstrate infiltration of different tissues and structures of the penis by tumoral cells, as determined by the rules of the UICC classification. CT was also helpless. The treatment of penile cancer consists of conservative methods using radiotherapy and chemotherapy. Amputation of the penis is always avoided when possible. So, cancer of the penis should be almost always classified according to findings of physical examination. There is no diagnostic need for CT in examining the penile lesions. In the present study, all penile tumours were determined by palpation while some tumours were completely missed by CT scans. Physical examination and CT findings concurred nevertheless in 62% of penile tumours.

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