Eur J Cancer, Vol. 27, No. 7, pp. 945–946, 1991.
Printed in Great Britain
0277–5379/91 $3.00 + 0.00
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Phase I/II Evaluation of Effervescent and Enteric Coated Oral Pamidronate for Bone Metastases

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THE DISCOVERY of the action of bisphosphonates on osteoclast activity led to study of their role in the management of tumour-induced osteolysis and hypercalcaemia [1]. These encouraging preliminary results have been confirmed by many groups and bisphosphonates are now considered the treatment of choice for hypercalcaemia [2].

Most studies have been performed with intravenous bisphosphonates, as this class of compounds is poorly absorbed from the gut, with an average bioavailability of 1% [3]. Although large doses, relative to those used parenterally, have to be administered, oral pamidronate has been shown to reduce skeletal morbidity in patients with breast cancer and established bone metastases [4] and attention is now turning to the possibility of preventing metastatic bone disease. However, in addition to the problems of absorption, gastrointestinal toxicity secondary to the locally irritant effect of pamidronate on the gut mucosa occurs. For long-term administration, particularly adjuvant use, the level of toxicity with the current non-proprietary formulation of oral pamidronate is considered too high. We have studied the toxicity and efficacy of two new oral formulations: an effervescent tablet and an enteric-coated capsule (Ciba-Geigy, Basle), in patients with bone metastases.

79 patients were treated with oral pamidronate at six hospitals. The median age was 56 years and all but 3 patients had advanced breast cancer. Eligibility required radiographically confirmed bone metastases and during the 1 month trial period patients received no other anticancer drug therapy. The exceptions to this were patients on endocrine treatment, providing this had not been changed in the previous 4 months, who continued with this treatment for the month to exclude the possibility of a withdrawal response. In addition, a raised level of urinary calcium excretion was necessary. This was defined as a urinary calcium/creatinine ratio (UCCR) of more than 0.4 (mmol/mmol) in fasting morning spot urine samples taken on two occasions during the week before trial entry.

Patients receiving medication known to affect bone metabolism, active peptic ulceration, intra-abdominal or cerebral metastatic disease, hypercalcaemia or gastrointestinal symptoms for any cause, were excluded. No patient had received previous long-term treatment with any of the bisphosphonates.

46 patients received the effervescent tablet and 33 the enteric-coated capsule. In any one centre all patients were treated with the same formulation. Each tablet, both effervescent and enteric-coated, contained 150 mg pamidronate disodium. For both formulations the patients were instructed to take pamidronate at least half an hour before food or any milk-containing drinks, to minimise the binding of pamidronate to calcium in the gut. Every centre started with 3-4 patients at the lowest dose level of 150 mg and thereafter the daily dose was escalated in successive cohorts by increments of 150 mg daily. In the first cohort 32 patients received 150 mg of pamidronate daily and subsequent cohorts received doses of 300 mg (n = 27), 450 mg (n = 12) and 600 mg (n = 8) daily.

Treatment was given daily for 4 weeks and patients were evaluated weekly for toxicity. All adverse events were recorded. Before treatment, and at each weekly follow-up visit, a full blood count and standard biochemical tests of renal, hepatic and bone function were performed. A fasting morning sample (second voided) of urine for measurement of UCCR was also obtained each week. At the end of the study period pamidronate could be continued if this was thought to be in the interest of the patient.

Both the effervescent and enteric-coated formulations of pamidonrate were sufficiently absorbed to cause rapid suppression of UCCR. In terms of this parameter, there were no significant differences between the two formulations in either the frequency or time to achieving a normal UCCR. Although not a specific aim of the study, analysis of the data revealed no difference in efficacy between any of the four doses tested. In 47/77 (61%) patients the UCCR fell to the normal range within 1 week and became normal at some time during the 4 week period of study in 68/77 (88%) patients.

Adverse events considered to be related to pamidronate are shown in Table 1. Nausea and vomiting were the most common side-effects. Toxicity was dose-related and the maximum tolerable dose for each formulation was 300 mg. Patients receiving

Table 1. Reported adverse events considered possibly, probably or definitely related to pamidronate

	Effervescent (mg)		Enteric-coated (mg)	
	150–300	450–600	150–300	450–600
Nausea	8 (23%)	8 (23%)	2 (8%)	2 (22%)
Vomiting	5 (14%)	7 (64%)	2 (8%)	0
Dyspepsia/abdominal pain	3 (9%)	3 (27%)	2 (8%)	2 (22%)
Diarrhoea	2 (6%)	3 (27%)	1 (4%)	0
Other GI symptoms*	4 (11%)	2 (18%)	1 (4%)	1 (11%)
Other non-GI symptoms†	5 (14%)	1 (9%)	0	1 (11%)
Unacceptable toxicity‡	2 (6%)	3 (27%)	0	2 (22%)
No side-effects	21 (60%)	3 (27%)	19 (79%)	5 (55%)

GI = gastrointestinal.
*Other GI symptoms: anorexia (3 patients), oral mucositis (1), constipation (1), flatulence (1), hiccough (1) and taste disturbance (1).
†Other non-GI symptoms: headache (2), pruritus (2), rash (1), oedema (1) and meteorism (1).
‡Toxicity leading to premature discontinuation of pamidronate.

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Revised 18 Mar. 1991; accepted 20 Mar. 1991.

150–300 mg pamidronate daily tolerated treatment reasonably well but those receiving 450–600 mg daily had an unacceptable incidence of adverse events. The toxicities in patients receiving the effervescent tablet, at all dose levels, tended to be worse and in view of its inconvenient mode of administration, this formulation will not be studied further. 5 patients taking the effervescent formulation and 2 receiving the enteric-coated capsule stopped treatment because of poor tolerability.

Studies of oral pamidronate as an adjunct to systemic therapy are now indicated. Toxicity was infrequent with the enteric-coated capsule at a dose of 150–300 mg daily and is therefore suitable for further study. However, the search continues for an even better tolerated formulation.

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Eur J Cancer, Vol. 27, No. 7, p. 946, 1991.
Printed in Great Britain
0277-5379/91 $3.00 + 0.00
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Primary Squamous Cell Carcinoma of the Endometrium

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PRIMARY SQUAMOUS cell carcinoma of the endometrium is a rare and interesting malignancy which was first described by Fluhmann in 1928 [1]. Absence of a glandular carcinoma and no connection between the tumour and the stratified squamous epithelium of the cervix constitute diagnostic elements, frequently called Fluhmann criteria. Only 26 cases have so far been reported.

2 women (59 and 62 years old) with postmenopausal bleeding (1 also with pyometra) presented to our department. Fractional curettage showed squamous cell carcinoma of the endometrium with intact basal membrane. Both patients had a radical hysterectomy with bilateral lymphadenectomy. Microscopic examination showed that the endometrial cavity was lined by squamous epithelium, continuous with a normal endocervical mucosal layer. The exocervical epithelial lining showed no signs of malignancy in both pieces. The neoplastic squamous epithelium of the uterine cavity showed infrequent epithelial pearls, occasional intercellular bridges, 1 – 2 mitoses per high-power field, moderate keratinisation-forming cordons and scattered islands, and was regarded as a moderately differentiated squamous cell carcinoma. The tumour penetrated one third of the full thickness of the myometrium. The endometrium next to the squamous carcinoma showed proliferation. Meticulous sections of the cervix and endocervical canal and the examined lymph-nodes revealed normal histopathology.

It is believed that the totipotential cells lying beneath the columnar epithelium may be transformed to squamous metaplasia under the influence of senile involutions, pelvic irradiation, vitamin A deficiency, or a chronic irritating process such as pyometra, uterine prolapse or eversion, intrauterine device and external irritants which are potential precursors of squamous cell carcinoma [2]. As in our 2 cases, published reports reveal that this is a disease of the postmenopausal period [3]. Our 2 cases were in oestrogen deficiency, which has a prominent oncogenic role in the overall histogenesis of this kind of malignancy [4–6].

Clinically, primary squamous cell carcinoma of the endometrium does not differ significantly from the epithelial endometrial malignancies, but it carries a poor prognosis. Local invasion of the myometrium was 80% during the first surgical procedure. Endometrial squamous cell carcinoma has a shorter symptomatic period than endometrial adenocarcinoma and 5-year survival is less than 20% (56.3% for adenoachantoma and 35.3% for adenosquamous endometrial carcinoma). Although vaginal cytology permits earlier and accurate diagnosis, for definite diagnosis the cervix must be examined to exclude squamous cell carcinoma [7]. Once diagnosed, immunhistochemical markers (cytokeratin, [EMA]) must be looked for. It is difficult to determine the best treatment due to the limited number of cases reported. Hysterectomy alone or hysterectomy plus adjuvant radiotherapy (pre-operative or postoperative) is the common mode of therapy. Chemotherapy is not helpful. Surgical treatment is mandatory if feasible, but adjuvant radiotherapy does not improve the prognosis when myometrial invasion and distant metastases exist [8, 9]. Primary squamous cell carcinoma of the endometrium is more lethal than the other varieties. 7 deaths within 26 months and 6 surviving patients have been reported to date [10]. The survival of our 2 cases is 19 months and 6 years, respectively.

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Revised 15 Apr. 1991; accepted 18 Apr. 1991.

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