Pergamon

European Journal of Cancer Vol. 30A, No. 3, pp. 396–398, 1994

0959-8049/94 $6.00+0.00

0959-8049(93)E0051-Q

Symptoms and Signs in Metastatic Spinal Cord Compression: a Study of Progression From First Symptom Until Diagnosis in 153 patients

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The symptoms in metastatic compression of the spinal cord or cauda equine are described after a systematic recording of the sequence of symptoms in 153 patients. Radicular pain was predominant in patients with metastases located in the lumbar area, while the severity of motor symptoms was positively correlated with thoracic metastases. The most common initial symptom was radicular pain, followed, with decreasing frequency, by motor weakness, sensory complaints and bladder dysfunction. The progression of motor weakness influenced the probability of establishing the diagnosis of spinal cord compression by stepwise marked increased probability when patients lost gait function or progressed into total paralysis.

Key words: spinal cord compression, clinical symptoms, metastatic compression, radicular pain
Eur J Cancer, Vol. 30A, No. 3, pp. 396–398, 1994

INTRODUCTION

SYMPTOMS AND signs in metastatic spinal cord compression have been reported by several authors since 1928 [1], but most studies have been retrospective and none of the few prospective studies [2, 3] have focused on the sequence of symptoms in the development of spinal cord compression.

The aims of the present study were to describe the frequency and the progression of symptoms in metastatic spinal cord compression.

PATIENTS AND METHODS

During a period of 3½ years, we included 153 consecutive patients with a myelographic diagnosis of spinal cord or nerve root compression due to intraspinal metastases from a histologically verified known solid malignant tumour.

At the time of diagnosis, all the patients were questioned according to a predesignated questionnaire about the presence and duration of local back pain, radicular pain, motor symptoms, sensory symptoms and bladder dysfunction. The development of motor symptoms was described by three different periods: (1) time elapsing from the first sign of motor weakness until loss of gait function, (2) duration from loss of gait function until inability to move the legs and (3) interval from inability to move the legs until diagnosis. It was well known that not all of the patients went through all of the three periods before diagnosis.

Statistical methods

Data was analysed by graphical log-linear models for multi- and high-dimensional contingency tables[4], distinguishing between direct interactions on one hand and indirect or spurious relationships on the other by tests for zero partial association (conditional independence). Statistical tests were performed as exact conditional tests [5], using Pearson's χ^2 statistic and the so-called partial gamma coefficient based on Goodman and Kruskall's gamma rank correlation for two-way tables [6]. P values reported in the next section always refer to test statistics for zero partial association controlling for appropriate prior or intervening variables.

The time from occurrence of the first symptom to the date of diagnosis was analysed by Cox regression models for proportional hazard including additional symptoms as time-dependent covariates [7].

RESULTS

The study comprised 75 women with a median age of 64 years (range 36–88) and 78 men with a median age of 71 years (range 26–92). Cancer of the breast, prostate and the lung were the primary malignancies in 56, 43 and 27 patients, respectively; the remaining 27 patients had other histologically known tumours. The distribution of intraspinal metastases were cervical 7, thoracic 102, and lumbar-sacral 44.

Symptoms and signs

Figure 1 shows the frequency of the different symptoms: the initial symptoms and the symptoms at time of diagnosis. At time of diagnosis, 134 (88%) patients complained of local back pain. Radicular pain was more frequent in tumours localised in the lumbo-sacral area (91%) than in tumours localised in the thoracic region (69%; $P = 0.005$), while the severity of paresis was most pronounced in patients with metastases in the thoracic region ($P = 0.013$).

Evolution and tempo of progression

The median time of duration of symptoms before diagnosis was 40 days (range 1–300) for radicular pain, 21 days (range 1–300) for weakness of legs, 14 days (range 1–180) for sensory

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Revised 25 Oct. 1993; accepted 25 Nov. 1993.

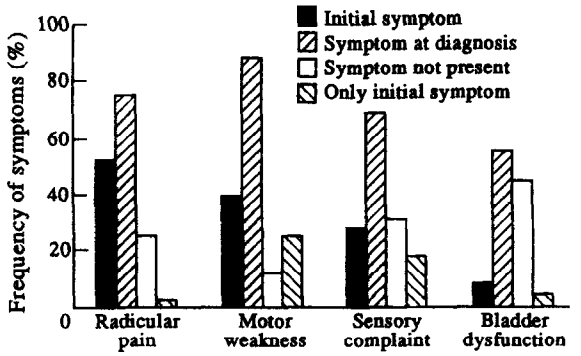

Fig. 1. Distribution of initial symptoms, presenting symptoms at time of diagnosis and symptoms presenting as monosymptomatic.

disturbances and 3 days (range 1–120) for bladder disturbances. Local back pain was not included in the analysis of duration of symptoms because local back pain is a common complaint in cancer patients with vertebral metastases without cord compression.

The time elapsing from the first symptom until diagnosis was analysed with regard to localisation of the spinal metastasis and appearance of other symptoms. The location of the metastasis had no bearing on the length of time between first symptoms and diagnosis. Radicular pain had only little diagnostic yield, i.e. the likelihood of having a myelography was not greater in patients with than in patients without this symptom. Appearance of sensory symptoms and bladder dysfunction facilitated the chance of myelography, but occurrence of motor weakness and gait disturbances were events that really hastened the diagnosis. Symptoms of motor weakness increased 3-fold the probability of having the diagnosis of spinal cord compression established compared to patients without motor symptoms. If the correct diagnosis was not established at this stage of disease, loss of gait increased the probability of the diagnosis 8-fold and total immobility 15-fold.

Figure 2 shows the interval from the first symptom of spinal cord compression until occurrence of motor symptoms. For all patients—including the 40% who had motor symptoms as the initial symptom—the median time until development of motor symptom was 7 days (range 0–212), and 80% of the patients developed motor symptoms within 2 months. Patients who had motor weakness among the initial symptoms had the diagnosis established within a significantly shorter time (30 days) than patients without motor disturbances among the initial symptoms (60 days) ($P = 0.012$, Wilcoxon).

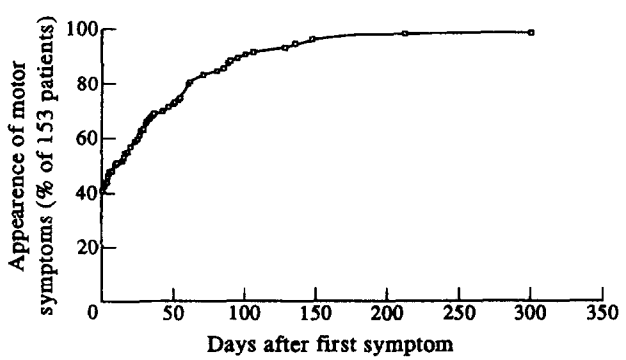

Fig. 2. Interval between first symptom of spinal cord compression and occurrence of motor symptoms (40% of the patients had motor symptoms among the initial symptoms).

In patients without gait function, the median time from the start of motor weakness until loss of walking ability was 38 days (range 0–140), and patients who progressed into paralysis did so within a median time of 12 days (range 0–19) after loss of walking ability.

DISCUSSION

The clinical picture of metastatic spinal cord compression is uniformly reported as pain, weakness, sensory loss and autonomic dysfunction [8–11]. The progression of symptoms has only been reported sporadically and reports of the overall duration of symptoms before diagnosis vary from days to years [10–12]. The main reason for this is probably that most studies have been retrospective, which makes it difficult to obtain a reliable history of the evolution of symptoms.

We found, as described previously [9, 10, 13], that the metastases were most frequently located in the thoracic area, and that the most frequent initial symptom was radicular pain, followed by, with decreasing frequency, motor symptoms, sensory symptoms and bladder dysfunction. The reason for the sequence of the symptoms is probably not due to the direction of the tumour growth from anterior and backwards [14], but rather that motor tracts may be functionally more sensitive to compression of the cord than the sensory tracts [15].

Radicular pain and sensory complaints were initial symptoms in patients with lumbar metastases, whereas weakness in the legs was more pronounced in patients with thoracic metastases. In the lumbar region, the roots run a very long course in a wide spinal canal and compression or traction of a single root can lead to radicular pain with minimal motor deficits. In contrast, metastases at the thoracic level will, owing to the narrow spinal canal, compress the spinal cord and affect the corticospinal tracts rather than the dorsal roots which have a very short intraspinal course. As the motor tracts are claimed to be more sensitive to compression than the sensory tracts [15], motor symptoms are more pronounced in thoracic metastases.

The presence of radicular pain did not significantly expedite the diagnosis, although root pain should be considered as a sign of traction or tumour infiltration of the nerve roots. The reason could be that the high frequency of pain complaints in cancer patients is blurring the clinician's awareness for changes in the pain pattern from local back pain to radicular pain, with characteristic exacerbation by coughing and sneezing. Moreover, radiating pain in the thoracic area can be mistaken as heart pain.

The probability for a diagnosis was markedly increased by the presence of motor symptoms, and the time from first symptoms to diagnosis was significantly shorter in the group of patients where motor symptom was the first symptom. However, some patients with motor symptoms were not diagnosed before they became paraplegic even in a case of progression over a considerable time.

We conclude that radicular pain in the legs as well as in the thoracic area is an important symptom, and this symptom as well as even minimal motor symptoms should always give cause for neuroradiological examination.

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Acknowledgements—This work was granted by the Danish Cancer Society, Torben Linnemanns Foundation for Cancer Research, Danish Hospital Foundation for Medical Research, Region of Copenhagen, the Faroe Islands, and Greenland, Foundation for Research in Neurology, the Foundation of Katrine and Viggo Skovgaard, Foundation of Fondsbørsvekselerer Henry Hansen and his wife Carla Hansen born Westergaard.

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European Journal of Cancer Vol. 30A, No. 3, pp. 398–400, 1994

0959–8049/94 $6.00+0.00

Amonafide as First-line Chemotherapy for Metastatic Breast Cancer

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In a phase II study, 32 patients with advanced breast cancer previously unexposed to palliative cytotoxic chemotherapy were treated with amonafide, 800–900 mg intravenously over 3 h repeated every 4 weeks. Objective response was seen in 8 patients including 1 complete response, 10 patients had stable disease and 14 patients progressed so the overall response was 25% (95% confidence interval, 11–43%). The most frequently encountered side-effects were haematological (granulocytopenia ≥ WHO grade 3 was encountered in 7/24 patients at 800 mg/m² and in 3/8 patients at 900 mg/m² amonafide) and nausea/vomiting (62%), despite prophylactic use of ondansetron. Non-haematological severe adverse reactions included neurotoxicity WHO grade 3 in 1 patient and orthostatic hypotension WHO grade 4 in another. In summary, the results of this trial suggest a limited therapeutic index of amonafide if used at this dose with this administration schedule.
Eur J Cancer, Vol. 30A, No. 3, pp. 398–400, 1994

INTRODUCTION

AMONAFIDE, A new synthetic imide derivate of naphtalic acid with both DNA intercalative properties and effects on macromolecular synthesis [1], has shown significant activity against intraperitoneally implanted murine leukaemias and solid tumour models [2]. Fairly good tolerance of the compound with myelosuppression as the dose-limiting toxicity has been reported in phase I/II trials [3–8], but whereas only modest antitumour activity has been noted in several different solid tumour types [4–8], encouraging therapeutic results were recently reported in metastatic breast cancer [9,10]. The preliminary findings of the Cancer and Leukemia Group B (CALGB) in previously untreated patients [9], and our own data yielding an 18% overall response rate in patients with advanced refractory disease [10], along with the predictable and reversible toxicity profile of the compound, encouraged us to initiate the present phase II trial of amonafide as first-line therapy in patients with metastatic breast cancer.

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Revised 23 Aug. 1993; accepted 22 Sep. 1993.

PATIENTS AND METHODS

Patients were eligible for this study if they had progressive, histologically confirmed, metastatic breast cancer. Additional criteria included: bidimensionally measurable disease, age ≤ 72 years, World Health Organization (WHO) performance status ≤ 1, leucocyte count ≥ 4000/μl, platelet count ≥ 100 000/μl,