Eur J Cancer, Vol. 26, No. 11/12, pp. 1133–1136, 1990.
Printed in Great Britain

0277-5379/90 $3.00 + 0.00

Specialist Interest Articles

Quality of Life and Treatment of Hormone Resistant Metastatic Prostatic Cancer

Sophie D. Fosså, Neil K. Aaronson, Don Newling, P.J. van Cangh, Louis Denis, Karl-Heinz Kurth, Marleene de Pauw and the members of the EORTC Genito-Urinary Group

72 patients with hormone resistant, progressing prostatic cancer completed a self-administered questionnaire to assess subjective morbidity and quality of life before they were entered into a phase III trial of estramustine (34) vs. mitomycin (38). At least one post-treatment assessment was available in 43 patients. This considerable degree of non-compliance is explained by practical problems related to completion and collection of the questionnaires in these rapidly deteriorating patients. Doctors underestimated subjective morbidity (pain, decreased performance status, nausea) in 30–50% of the cases. Decreased functional status, fatigue and pain were identified as the most frequent major morbidities before study entry. In most patients, treatment did not reduce this morbidity. The routine application of self-administered quality of life questionnaires has considerable practical problems but yields clinically worthwhile information about subjective morbidity. Simple but relevant monitoring of subjective morbidity by the patient should be mandatory in cancer trials where palliation is a major endpoint.
Eur J Cancer, Vol. 26, No. 11/12, pp. 1133–1136, 1990.

INTRODUCTION

IN AT LEAST 50% of patients with prostatic cancer the malignancy becomes hormone resistant. This condition is defined as progressive disease after primary hormonal manipulation which has achieved serum testosterone levels within the castration range. Many of these patients will develop painful bony metastases, others will have a decreased performance status. With survival as the primary endpoint, systemic treatment with cytostatic drugs and/or secondary hormonal manipulation has, so far, not been very successful [1–3]. Palliation of symptoms has been achieved in some patients, but there is considerable doubt about the degree of subjective relief and the superiority of any drug in achieving symptomatic relief.

In 1986 the Genito-Urinary (GU) Group of the European Organization for Research and Treatment of Cancer (EORTC) started a phase III trial in patients with hormone resistant prostatic cancer to compare estramustine with mitomycin. Time to progression and duration of overall survival were the major endpoints. Within this protocol the use of self-administered questionnaires on quality of life was optional. We report the group's experience with such questionnaires as regards feasibility and results on subjective morbidity and quality of life.

Correspondence to S.D. Fosså.
S.D. Fosså is at the Norwegian Radium Hospital, Montebello, N-0310 Oslo 3, Norway; N.K. Aaronson is at the Netherlands Cancer Institute, Amsterdam, The Netherlands; D. Newling is at the Princess Royal Hospital, Hull, U.K.; P.J. van Cangh is at the St Luc University Hospital and M. de Pauw is at the EORTC Data Center, Brussels, Belgium; L. Denis is at the Academic Hospital Middelheim, Antwerpen, Belgium; and K.H. Kurth is at the Academic Medical Hospital, Amsterdam, The Netherlands.

PATIENTS AND METHODS

Patients

Twenty-nine institutions entered 171 patients with progressing, hormone resistant prostatic cancer into EORTC protocol 30865 (study coordinator D.N.). Patients were randomised either to receive mitomycin 15 mg/m^2 every 6 weeks or estramustine 280 mg twice daily orally (with the possibility of increasing this dose to 720 mg daily if tolerated). The trial was closed in April 1989. Up to April 1990, 9 patients had been deemed ineligible. We report on the remaining 162 patients.

Doctor's assessments

The doctor completed EORTC patient forms before treatment and every 6 weeks. These forms included clinical findings with biochemical and radiological results. The doctor's evaluation of the patient's performance status was done according to WHO: no impairment (0), slight impairment, but ambulatory (1), less than 50% confined to bed/chair (2), more than 50% confined to bed/chair (3) and completely confined to bed/chair and help needed for daily basic functions (4). The pain level was scored as follows: no analgesics (0), non-narcotic analgesics used irregularly (1), non-narcotic analgesics used regularly (2), narcotic analgesics used irregularly (3) and narcotic analgesics used regularly (4). During follow-up any increase of the dose of analgesics was monitored. Vomiting and nausea during treatment were recorded (yes/no).

Questionnaires

As an option, patients were asked at each attendance to fill in a questionnaire on functional status, social role functioning,

Table 1. Patients' evaluation of pain and analgesic treatment

Use of analgesics	Pain: Not at all/ a little	Pain: Quite a bit/ very much	Total
None/non-narcotics	22	15	37
Narcotics	8	22	30
Total	30	37	67

gastrointestinal morbidity, fatigue/malaise, sexuality, urological symptoms, pain, psychological distress and social activity (Appendix 1). This questionnaire was based on that developed by the EORTC Quality of Life Study Group [4].

Pre-treatment, investigators from thirteen institutions opted to take part in the quality of life section of the protocol. 72 patients (group 1) filled in a pretreatment questionnaire (38 patients from the mitomycin arm, 34 from the estramustine arm). Biochemical and radiological indices in these patients were statistically not different from those in the 90 patients without quality of life questionnaires before treatment (group 2). However, significantly more patients in group 1 had received palliative radiotherapy and were using narcotics at study entry.

During treatment, at least one follow-up questionnaire was available for 43 patients as follows: 6 week evaluation, 31 patients; and 3 month evaluation without 6 week assessment, 12 patients. 29 patients never provided a post-treatment questionnaire. The reason for these patients' non-compliance is not known, but the most frequent cause was probably deterioration of the patient's general condition. 19 of the 31 patients evaluable at 6 weeks went off study at this time; 12 continued on treatment and were analysed with the 12 who had completed a questionnaire at 3 months but not at 6 weeks. 7 of these 24 patients discontinued their trial treatment after 3 months due to progression/toxicity, while 17 patients continued on treatment.

Statistics

We used χ^2 and Wilcoxon matched-pairs signed-rank tests.

RESULTS

Doctor's vs. patient's assessment of subjective morbidity

28 patients indicated in their pretreatment questionnaire that they needed help for such basic daily functions as eating, dressing and washing, and/or were confined to bed or to the chair most of the day due to their malignancy. However, in only 8 of these patients did the doctor recognise this major disability and report a performance status of 3 or 4. In 12 of these patients the clinician recorded a performance status of 2 and in the remaining 8, performance status was recorded to be 0 or 1.

37 of 67 evaluable patients recorded considerable pain on entry to the trial despite the fact that 22 had been prescribed narcotic analgesics (Table 1). At first follow-up attendance 8 of 23 patients still indicated insufficient pain relief despite analgesic treatment.

13 of 41 responding patients reported that they had suffered from significant (quite a bit, very much) nausea in the week preceding their first follow-up examination. The doctor reported this symptom for only 8 of them.

Table 2. Patients' major pretreatment morbidity (n = 72) *(quite a bit, very much)*

Morbidity	No. of patients
Decreased functional status	29 (40%)
Fatigue	31 (43%)
Pain	36 (50%)
Psychological distress	7 (10%)
Reduced social activity	15 (21%)
Urological symptoms	0

Table 3. Effect of treatment upon major pretreatment morbidity in patients completing questionnaires

Follow-up	No. of patients: Pretreatment	No. of patients: After treatment
6 weeks, 31 evaluable patients		
Reduced functional status	9 (29%)	11 (35%)
Fatigue	16 (52%)	21 (68%)
Pain	16 (52%)	19 (61%)
Nausea/vomiting	1 (3%)	7 (23%)
3 mo, 24 evaluable patients		
Reduced functional status	8 (33%)	8 (33%)
Fatigue	11 (46%)	12 (50%)
Pain	14 (58%)	15 (63%)
Nausea/vomiting	1 (4%)	2 (8%)

Major pretreatment morbidity

Decreased functional status, fatigue and pain were the most frequently mentioned major complaints in the patients' pretreatment questionnaires (Table 2), followed by reduced social activity and psychological distress. Major urological symptoms did not seem to be a problem in these patients.

Effect of treatment

The limited number of post-treatment questionnaires did not allow statistical comparison between the two treatments. Patients from both groups were therefore combined. There was no reduction in number of patients with major complaints during treatment and at 6 weeks a tendency for more patients to have major complaints (Table 3). The number of patients with gastrointestinal morbidity increased, probably due to treatment-induced toxicity. The post-treatment situation was more stable for the patients who received treatment for 3 months, but without reduction of the number of patients with major complaints (Table 3).

DISCUSSION

There was considerable non-compliance in completion of the questionnaires. Completion was optional and represented the GU Group's first attempt to assess quality of life in patients with urological cancer. Most urologists were, when the trial started, not used to assessing systematically quality of life in their patients. Few clinicians were willing to make the regular necessary effort. They probably did not feel confident that this type of assessment would provide any information of value to add to that from clinical, biochemical and radiological examination.

The clinician's commitment is an indispensable condition for quality of life assessments. Even though this condition is fulfilled, it may still be difficult to include all available patients in quality of life studies. The thirteen institutions that opted to participate in the current study entered 90 patients in the protocol, but only 72 of these patients completed pretreatment questionnaires. The reason for this non-compliance is not known. Lack of time needed to assist patients with the completion of the questionnaires, might have been important. We have shown that 24% of similar patients needed help for a median of 12 min (range 1–20) to fill in the forms used in this study [5]. Only a few clinicians have a research nurse who can assist patients with questionnaire completion. Even if sufficient help can be given, patients with a rapidly progressing malignancy often have great difficulties in answering lengthy quality of life questionnaires [6].

Our reluctance to use self-administered questionnaires for assessment of subjective morbidity was also related to the lack of validity and reliability of previously used instruments. However, clinicians, psychologists and sociologists have developed questionnaires which, although still not completely satisfactory, can validly assess subjective morbidity and quality of life from the patient's point of view [4,7]. Tannock *et al.* [8] obtained clinically worthwhile and valid information from patients' questionnaires during the treatment of hormone resistant prostatic cancer.

We concentrated on frequent symptoms of somatic morbidity, such as changes of general condition, pain, and urinary and gastrointestinal dysfunction. Most clinicians feel confident in the assessment of the relevant symptoms and record them on the patients' record forms. The assessment of psychological morbidity might, on the other hand, represent a more complicated task for a busy clinician. We used the first version of the EORTC quality of life questionnaire and added a disease specific module on urological symptoms. The general part of the questionnaire has been found to be reliable and valid in lung cancer patients [4]. The design of our questionnaire with regard to the individual questions is similar to that of the Rotterdam symptom check-list, which is recommended as the current "best-bet" by the Quality of Life Group of the Medical Research Council [7].

Pain relief and improvement of general well-being are important aims in the treatment of hormone resistant cancer of the prostate [9,10]. This was confirmed in the present study which showed that pain and fatigue are the most frequent major complaints in these patients before and during treatment. Reduction of pain and improvement of fatigue should thus be endpoints in clinical trials in these patients. As yet, few studies that consider the patients' self-assessment of these and other quality of life variables have been reported in patients with prostatic cancer [5,8,10–12].

Our observation on pretreatment subjective morbidity should be considered with some caution since only 40% of the patients entered in the trial completed a pretreatment questionnaire. We cannot exclude the possibility that these patients may represent a negatively selected subgroup, despite the comparability of most of the clinical and biochemical variables; more patients in group 1 had undergone palliative radiotherapy and more used narcotic analgesics. On the other hand, these differences may be due to different attitudes to narcotic analgesics and radiotherapy between institutions.

Our results are consistent with those of others [13–16] showing great variations between the patient's and the doctor's evaluation of performance status, pain and pain relief. This may have significant therapeutic consequences. If the patient's complaints are not recognised adequately, they are often not sufficiently treated, as was the case for pain in 8 of our 23 follow-up patients. Furthermore, underestimation of symptoms by the doctor may lead to patient dissatisfaction with the health service [16].

Due to the limited number of patients completing follow-up questionnaires, no statistically meaningful comparison of the palliative effect of the two treatments could be made. However, no large differences were evident for effectiveness or toxicity. The results from the self-administered questionnaires are thus consistent with the preliminary report of this trial which demonstrated the limited effectiveness of both drugs and a high toxicity [17].

Our results may give some guidance on the key questions that should be asked in future. Pain, impaired performance status and fatigue were the most frequent areas of major concern, which confirmed preliminary results from a single institution [5]. In future, questionnaires should include those areas in particular and also assessment of expected subjective treatment-related toxicity. Furthermore, a better scoring system for the doctor's evaluation of pain should be developed; recording the use of analgesics, their type and doses, as we did, is not sufficient, since it does not indicate whether the treatment has achieved satisfactory pain relief. Furthermore, self-administered questionnaires for this type of patient should be simple and short, but nevertheless contain significant and relevant questions to enable assessment of subjective morbidity.

1. Eisenberger MA, Simon R, O'Dwyer PJ, Wittes RE, Friedman MA. A reevaluation of nonhormonal cytotoxic chemotherapy in the treatment of prostatic carcinoma. *J Clin Oncol* 1985, **3**, 827–841.
2. Raghaven D. Non-hormone chemotherapy for prostate cancer: principles of treatment and application to the testing of new drugs. *Semin Oncol* 1988, **15**, 371–389.
3. Fosså SD. Second line treatment in prostatic cancer: hormonal and cytostatics. In: Bloom HJG, Hanham IWF, eds. *Urological Oncology: Dilemmas and Development*. Chichester, Wiley, 1988.
4. Aaronson NK, Bakker W, Stewart AL, *et al.* Multidimensional approach to the measurements of quality of life in lung cancer clinical trials. In: Aaronson NK, Backmann, eds. *The Quality of Life of Cancer Patients*. New York, Raven Press, 1987, 63–86.
5. Fossà SD, Aaronson N, da Silva CP, *et al.* Quality of life in patients with muscle-infiltrating bladder cancer and hormone-resistant prostatic cancer. *Eur Urol* 1989, **16**, 335–350.
6. Ganz PA, Haskell CM Figlin RA, La Soto N, Siau J. Estimating the quality of life in clinical trial of patients with metastatic lung cancer using the Karnofsky performance status and the functional living index-cancer. *Cancer* 1988, **61**, 849–856.
7. Maguire P, Selby P. Assessing quality of life in cancer patients. *Br J Cancer* 1989, **60**, 437–440.
8. Tannock I, Gospodarowicz M, Meakin W, Panzarella T, Stewart L, Rider W. Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol* 1989, **7**, 590–597.
9. Fosså SD, Aaronson N, and the members of the EORTCC GU Group. Treatment aims in hormone-resistant prostatic cancer. In: *Oncology: Present and Future* (Pais 131189). Proceedings (in press).
10. Presant CA, Soloway MS, Klioze SS, *et al.* Buserelin treatment of advanced prostatic carcinoma. Long-term follow-up of antitumor responses and improved quality of life. *Cancer* 1982, **59**, 1713–1716.
11. Parmar H, Phillips RH, Lightman SL, Edwards L. How would you like to have an orchiectomy for advanced prostatic cancer? *Am J Clin Oncol* 1988, **11**: S160–S168.
12. Smith JA. Palliation of painful bone metastases from prostate cancer using sodium etidronate: results of a randomized, prospective double-blind, placebo-controlled study. *J Urol* 1989, **141**, 85–87.
13. Nelson E, Conger B, Douglass R, *et al.* Functional Health status levels of primary care patients. *JAMA* 1983, **249**, 3331–3338.
14. Slevin ML, Plant H, Lynch D, Drinkwater J, Gregory WM. Who

should measure quality of life, the doctor or the patient? *Br J Cancer* 1985, **57**, 109–112.
15. Grossman SA, Sheidler VR, Swedeen K, Mucinski J, Piantadosi S. Lack of correlation of patient (PT) and health care provider (HCP) ratings of cancer pain severity. *Proc ASCO* 1990, **9**, 338.
16. Wartman SA, Morlock LL, Malitz FE, Palm E. Impact of divergent evaluations by physicians and patients' complaints. *Public Health Rep* 1983, Vol 98, 141–145.
17. Newling D, Fossà SD, Tunn U, Kurth KH. The comparison of the effects of high dose estramustine phosphate and mitomycin C on the time to progressive, advanced endocrine independent prostatic cancer: an analysis of EORTC GU Group Study No. 30865. *J Steroid Biochem* (in press).

Acknowledgements—We thank Harald Aagedal for assistance with data management and Dr Stein Kaasa for valuable comments.

APPENDIX

QUALITY OF LIFE QUESTIONNAIRE FOR EORTC PROTOCOL 30865

We are interested in some things about you and your health. There are no "right" or "wrong" answers. Please answer all the questions yourself by circling the number that best applies to you. The information that you provide will remain strictly confidential.
Please fill in today's date: Day _____ Month _____ Year _____

Because of your present condition:	Yes	No
1. Do you need help with eating, dressing, bathing or using the toilet?	1	2
2. Do have to stay in bed or a chair for most of the day?	1	2
3. Do you have to stay indoors most or all of the day?	1	2
4. Do you have any trouble either walking a short distance or climbing one flight of stairs?	1	2
5. Do you have any trouble either taking a walk or climbing a few flights of stairs?	1	2
6. Do your have any trouble bending, lifting or stooping?	1	2
7. Are you limited in any way in doing your work or household jobs?	1	2
8. Does your condition keep you from working at a job or doing household jobs?	1	2

During the past week:	Not at all	A little	Quite a bit	Very much
9. Did you have to urinate more frequently than normal for you?	1	2	3	4
10. Did you have difficulty controlling your urination?	1	2	3	4
11. Did you pass blood when you urinated?	1	2	3	4
12. Did you have pain when you urinated?	1	2	3	4
13. Did you have pain in other parts of your body?	1	2	3	4
14a. Did you have any treatment for pain? No 1 Yes 2	1	2	3	4
14b. How much did it help?	1	2	3	4
15. Did you lack appetite?	1	2	3	4
16. Were you nauseated?	1	2	3	4
17. Did you vomit?	1	2	3	4
18. Did you feel energetic?	1	2	3	4
19. Were you physically well?	1	2	3	4
20. Were you tired?	1	2	3	4
21. Did you need to rest?	1	2	3	4
22. Did you have any trouble sleeping?	1	2	3	4
23. All in all, did you feel ill?	1	2	3	4
24. Did your condition limit your interest in sex?	1	2	3	4
25. Were you limited in your ability to have or maintain an erection?	1	2	3	4
26. Did your condition interfere with your enjoyment of sex?	1	2	3	4
27. Did you feel tense?	1	2	3	4
28. Did you feel irritable?	1	2	3	4
29. Did you feel lonely?	1	2	3	4
30. Did you worry?	1	2	3	4
31. Did you feel depressed?	1	2	3	4
32. Has your condition interfered with your family or social life?	1	2	3	4
33. Has your medical treatment interfered with your family or social life?	1	2	3	4

PLEASE CHECK TO MAKE SURE THAT YOU HAVE ANSWERED ALL OF THE QUESTIONS