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Symptoms, Symptom Distress and Health-related Quality of Life in Patients with Polycythaemia Vera or Essential Thrombocythaemia during Treatment with Interferon-alpha

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Acta Oncologica Vol. 41, No. 1, pp. 50–55, 2002

Sixteen patients with polycythaemia vera or essential thrombocythaemia were treated with interferon-α in order to normalize elevated platelets. Patients were followed for 6 months and the frequency and intensity of symptoms and side effects were recorded before and during the study period by the patients and by the doctor. Health-related quality of life was also assessed. The most frequently reported pretreatment symptoms were fatigue, headache and muscle pain. The intensity of fatigue initially increased during treatment and there was no relief of any of the three most frequent symptoms during the treatment period. Common interferon-related symptoms such as fever and chills were most frequently reported after one week. After one month of treatment, symptoms related to the gastrointestinal tract reached a peak. Two patients discontinued treatment during the study period. Another patient suffered severe depression after the study period when still on interferon. There was no difference between the frequency of symptoms recorded by the doctor and that reported by the patients.

Received 10 October 2000
Accepted 27 September 2001

Polycythaemia vera (PV) and essential thrombocythaemia (ET) are clonal disorders (1) characterized by aberrant proliferation of erythroid, myeloid or megakaryocytic cells in the bone marrow and an increased cell count in the peripheral blood. Clonal thrombocytosis is typical of ET and is also observed in 50–80% of patients with PV (2). Patients with PV and ET have an increased incidence of thromboembolic complications and bleedings that can sometimes be fatal. The disorders are accompanied by fibrosis of the bone marrow, and in the final stage, severe myelofibrosis may occur with deficiencies of all blood cells (3). There is also an increased risk of developing acute leukaemia. This risk is higher in PV than in ET (4).

Many patients in the early stages of PV and ET receive treatment in order to normalize the haemoglobin and the platelet counts. Phlebotomies are effective in reducing the erythrocyte volume. Radioactive phosphorus and cytotoxic drugs, such as busulphan, are also useful but several studies have shown that mutagenic substances can increase the incidence of acute leukaemia. Data also indicate that treatment with hydroxyurea can increase the risk for leukaemic transformation (5, 6). More recently, anagrelide has provided a new tool to reduce platelets in PV and ET. This drug is not mutagenic but it should be used with caution for patients with heart disease and is not recommended for use during pregnancy (7).

Interferon-α is effective in normalizing elevated platelet counts in PV and ET and usually reduces the need for phlebotomies in PV (8, 9). Interferon-α is an endogenous substance with no known mutagenicity and it is therefore commonly used for young patients with ET and PV who require treatment. It can also be used during pregnancy. It is known that treatment with interferon-α causes significant side effects and requires that repeated injections be given (10–12). However, how patients with these particular disorders perceive the side effects of the treatment and

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how this may influence the patients' health-related quality of life (HRQL) have to our knowledge not been studied before.

The aims of this study were to describe the self-reported symptoms, intensity and distress of perceived symptoms and the HRQL in patients with PV or ET before and during treatment with interferon-α. Moreover, we sought to compare the obtained data regarding the self-reported HRQL with similar data from a Swedish reference group. We also wanted to compare the frequency of symptoms reported by the patients with the frequency of symptoms noted by the doctor in the patients' medical records.

MATERIAL AND METHODS

Patients

Sixteen patients (4 males, 12 females) from Huddinge University Hospital, Södertälje Hospital and Umeå University Hospital in Sweden were consecutively included in the study; 9 patients had PV and 7 patients had ET. The median age was 58 years and the age distribution was 19 to 75 years. Highly purified leucocyte interferon-α manufactured by BioNative AB, Umeå, Sweden was used in the study. Interferon treatment was given as subcutaneous injections and administered by the patients, after a nurse had given them some initial training. The initial dose was 3 million units 5 to 7 times weekly and the dose was adjusted to the lowest tolerated dose to achieve a platelet count below 400×10^9/L. Patients were instructed to take paracetamol before injections at the onset of therapy and to continue this medication as long as flu-like symptoms occurred.

For patients with PV, phlebotomies were performed when the erythrocyte volume fraction exceeded 48%. Acetylsalicylic acid (ASA) was administered to patients with symptoms of platelet aggregation or platelet counts exceeding 1000×19^9/L.

Instruments

Two questionnaires were used for the study. The SFID-interferon questionnaire (Symptom, Frequency, Intensity, Distress) is a modification of a questionnaire developed by Gardulf, Larsen and Nordström for patients undergoing bone-marrow transplantation (BMT). This questionnaire was modified to cover the known systemic side effects of interferon-α therapy. The 11 therapy-induced symptoms asked for were nausea, fever, chills, headache, joint or muscle pain, fatigue, diarrhoea, constipation, loss of appetite, depression and hair loss. The SFID-interferon questionnaire consisted of 16 items and the patients were primarily asked if they had perceived the symptoms asked for (response scale 'none' to 'much'). Secondly, the patients were asked to rate how intense and, thirdly, how distressful the perceived symptoms were. The response scale ranged from 0 ('none') to 3 ('Yes, very much'). Five questions measured general well-being, perceptions of therapy and the willingness to continue the treatment. The SFID-interferon questionnaire was completed by the patient at home, before initiation of the therapy and after 1 week, 1 month and 6 months of treatment. These timepoints were chosen in order to cover acute side effects as well as long-term perception of treatment. The SFID scale has been used for long-term follow-up after BMT (13) and for patients with multiple sclerosis treated with interferon-β (14).

The Swedish Health-Related Quality of Life Questionnaire (SWED-QUAL) is a generic HRQL questionnaire designed for use in both chronically and acutely ill subjects. The SWED-QUAL, which was developed by Brorsson et al. (15), measures the patient's self-rated HRQL and includes 68 items forming a total of 13 subscales: physical functioning, satisfaction with physical functioning, pain, role limitations caused by physical and emotional health problems, emotional well-being (i.e. positive effect and negative effect), perceived degree of cognition/vitality, sleep functioning, satisfaction with family life, satisfaction with relationship to partner, sexual functioning and general health perception. The answers to the multi-items were given on Lickert-type scales with four answer options. Each scale is transformed into a 0–100 index —the higher the score, the better the patient's self-rated HRQL. The SWED-QUAL has been standardized in a large Swedish study and was found to be of good psychometric quality (15). The form was filled in before and during therapy with interferon-α. The results were compared with answers given by a Swedish reference group comprising a randomly selected sample of individuals ($n = 2\,866$) from the Swedish population aged between 18 and 84 years (15).

Case record form

The patients were seen by their doctors before treatment and at 1, 2, 3 and 6 months of treatment. At each visit, the occurrence and intensity of symptoms were recorded in a case record form by the doctor and later compared with the patients' reports.

Statistical methods

Non-parametric methods were used, as we found that the variables were not normally distributed. The sign test was applied to evaluate differences in the occurrence of symptoms in paired samples. To evaluate the degree of symptoms, the Friedman test and the Wilcoxon signed-ranks test, were used.

Ethical considerations

The patients were given both written and oral information about the study and informed consent was obtained from those participating. The local Ethics Committee at Huddinge University Hospital approved the study.

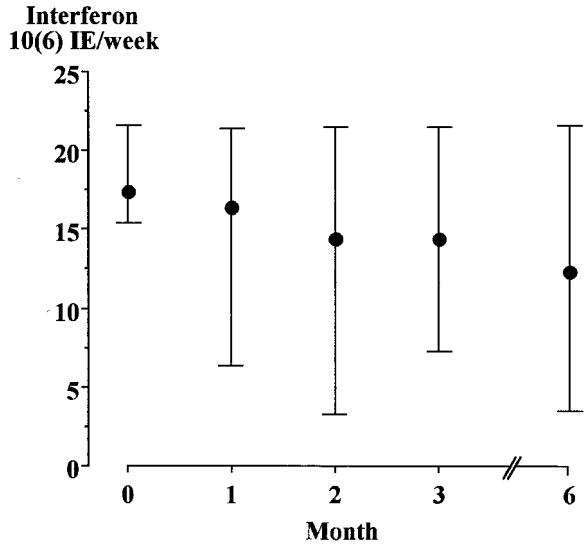

Fig. 1. The spread and mean of the weekly dose of interferon-α at different time-points.

RESULTS

Treatment and response to therapy

The average platelet count at the start of treatment was 1017×10^9/L (range $772–1648 \times 10^9$/L). The average platelet count was 613×10^9/L at one month, 537×10^9/L at 3 months and 441×10^9/L at 6 months.

The average dose of interferon-α was 17 million units per week at the start of the study. The dose was reduced continuously, as indicated in Fig. 1. At 6 months, the average dose was 12 million units per week.

During the 6-month study period, the therapy was discontinued by two of the patients. One patient decided to interrupt the study after two months, owing to several side effects and a feeling of depression. The other patient was withdrawn from the study at two months, owing to inability to deal with the injections.

There were no thromboembolic complications or episodes of major bleeding during the study period.

Reported symptoms

As illustrated in Fig. 2, the patients reported several symptoms even before the initiation of the interferon-α therapy. The most frequently reported symptoms were headache, muscle pain, fatigue and depression, which were reported by more than 30% of the patients.

Fever, chills, headache, muscle pain, fatigue and depression were reported by at least half of the patients in the first week. The reported increase in chills was statistically significant ($p = 0.039$) but was reported to decrease after one month ($p = 0.01$). Nausea, loss of appetite and diarrhoea were reported by more than half of the patients in the first month.

The intensity of fatigue was significantly increased after 1 month as compared with the intensity before treatment ($p = 0.03$) but at 6 months this intensity was reported to be significantly lower as compared with that at one month ($p = 0.036$). There was an increased frequency of diarrhoea at one month ($p = 0.03$). The patients reported an increase in hair loss at 6 months ($p = 0.035$) but no significant difference in frequency of depression during the treatment (Fig. 2).

Impact of symptoms on daily life

The patients were asked to indicate what impact the reported symptoms had on their daily life. In total, any

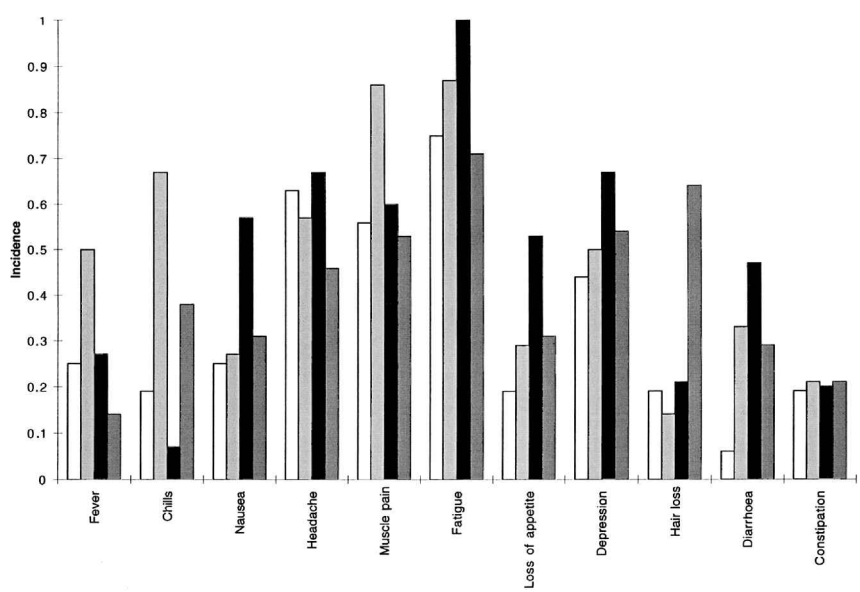

Fig. 2. Frequency of 11 symptoms reported by patients in the SFID-interferon questionnaire before treatment at 1 week, 1 month and 6 months of treatment. □ Before; ▒ 1 week; ■ 1 month; ▒ 6 months.

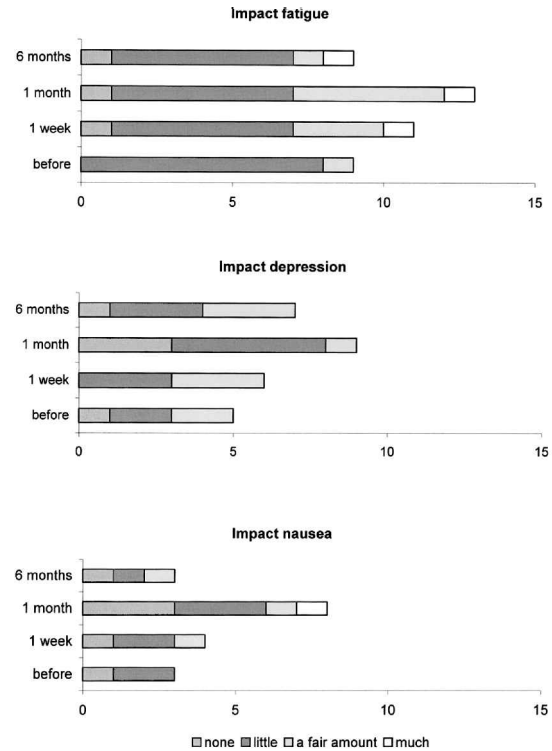

Fig. 3. The impact on daily life of fatigue, depression and nausea at different time-points. The bars indicate the number of patients who reported symptoms and the extent to which they affected their daily life.

type of symptom was reported on 206 occasions during the study period. No impact on daily life was reported in 33% of occasions, little impact in 46%, a fair amount in 15% and a considerable amount in 5% of occasions. The symptoms with the most severe impact on daily life, i.e. 'a fair amount' or 'a considerable impact', were fatigue, which was reported as being at this level of impact in 6% of all reported symptoms, and depression (4%), as shown in Fig. 3.

SWED-QUAL

There was no statistically significant difference in HRQL as measured by the SWED-QUAL among the patients before or during therapy with interferon-α, nor any difference between the patients and the reference group at any time point.

Comparison of symptoms reported by the doctors and by the patients

There were no statistically significant differences between the symptoms as reported by the doctors and the patients (Fig. 4).

The patients' perceptions of injections and therapy

The patients reported no or little discomfort in taking the injections. They perceived that the treatment had an effect on the disease and 12 out of 13 patients were anxious or very anxious to continue the treatment with interferon-α.

DISCUSSION

The main aim of this study was to evaluate the feasibility of treatment with interferon-α in patients with PV or ET and to record self-reported symptoms, intensity and distress of perceived symptoms and HRQL. Symptoms of PV and ET are often attributed to hyperviscocity in PV or dysfunction of platelets or abnormal platelet aggregation. Patients sometimes exhibit erythromelalgia with localized, painful lesions on the distal portions of the extremities. Patients are sometimes diagnosed after a major thromboembolic event or after an episode of excessive bleeding. However, many patients are diagnosed after routine laboratory tests when elevated haemoglobin levels or platelets are discovered. Symptoms in these patients are often discrete and not characteristic of the disease. In this study, a number of symptoms not usually attributed to the disease were reported by the patients before initiation of therapy.

Fatigue was a prominent symptom for the patients in our study. Fatigue was reported by 75% of the patients before the study and thus it seems to be a symptom of the disease itself. However, the study showed that the intensity of fatigue increases during treatment with interferon-α and was at its most intense after one month of treatment. Fatigue is the most persistent and pervasive symptom of interferon-α therapy (16).

Other symptoms that were frequently reported before treatment were headache and muscle pain. Muscle pain is also a common side effect during treatment with interferon-α and, as expected, it increased at the beginning of interferon treatment. Of the three most frequently reported symptoms before treatment—headache, fatigue and muscle pain—the frequency was similar to that at baseline at six months. Thus, there was no indication that interferon-α treatment relieved these symptoms associated with the disease.

Several other symptoms were reported during the study that can be related to the interferon-α treatment. Typical side effects of the therapy are fever and chills. These symptoms were most frequently reported at one week but were thereafter reported in a frequency similar to that at baseline. Somewhat unexpectedly, nausea, loss of appetite and diarrhoea were reported by more than 50% of the patients after one month of treatment. However, after 6 months these symptoms were less frequent. Another symptom that can be attributed to interferon-α was hair loss, which was most frequent at 6 months. Two patients had significant hair loss and this was the cause of interruption of therapy for one male patient after the study period.

There were no significant differences between the frequency of depression at the different time-points. Most patients had received their diagnosis just prior to the start

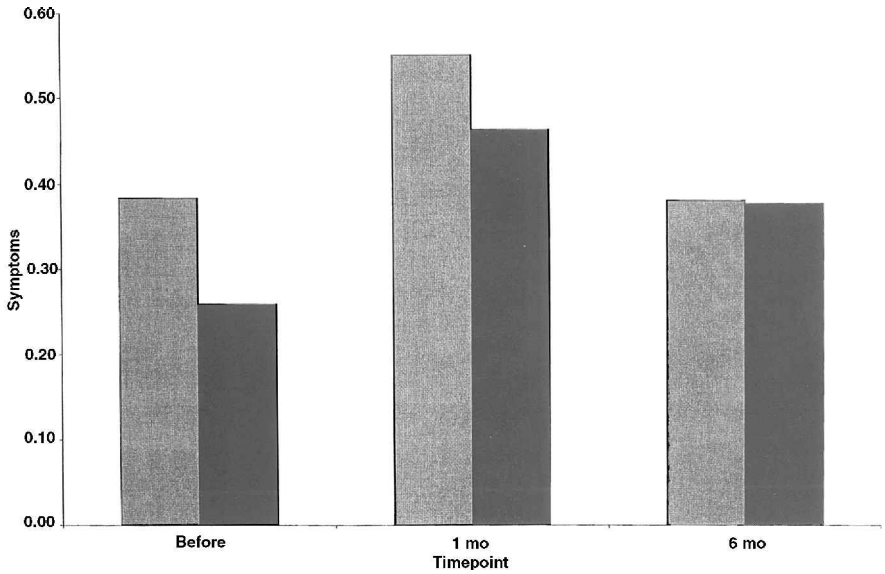

Fig. 4. Comparison of frequency of symptoms reported by patients in the SFID-interferon questionnaire and by the physician in the case-record form. Ten identical symptoms that were included in both the SFID-interferon questionnaire and the case-record form are used in the analysis. ■ Patient. ■ Doctor.

of the study, which could explain why depression was reported by 40% of the patients at baseline. One patient with a history of psychiatric illness was taken into hospital because of a severe attack of depression 8 months after the initiation of treatment. This patient had not reported any signs of depression at the start of treatment and reported mild depression after one week and one month and moderate depression at six months. Whether treatment with interferon-α contributed to her psychiatric illness is not clear, but treatment was discontinued. A second patient stopped treatment after 2 months because of depression and severe side effects.

SWED-QUAL could not detect any differences in quality of life during interferon treatment nor any difference in the patients compared with the reference group. Clearly, the small number of patients in this study could explain the lack of information obtained by SWED-QUAL. However, in SWED-QUAL, items are analysed in groups and changes regarding specific items could be outbalanced within each subscale. The SFID-interferon scale that was specifically constructed to look at common and expected side effects during interferon treatment, proved to be more sensitive in our study.

In this study symptoms were recorded separately by both the patients in questionnaires and by the doctors in case-record forms based on observations during the patient's visit to the doctor. At the beginning of the study there were fewer observations of symptoms recorded by the doctors but there was no statistical difference. At 6 months the frequency of symptoms reported by the doctor was almost identical to that reported by the patients themselves. Thus, it seems that the symptoms asked for were relevant and concrete enough to obtain a high level of agreement between the doctor and the patients. Good overall agreement between doctors and patients has also been reported in previous studies where patients were asked to rate symptoms (17). It has been found that the level of agreement between healthcare providers and patients appears to be dependent on clear questions with a high degree of concreteness and a minimum of subjectivity in the quality of life dimensions assessment. For example, patients' functional status tends to be more accurately rated than patients' level of psychological distress (18–20).

This study shows that treatment with interferon-α is efficient and well tolerated by the majority of patients below 75 years of age with PV or ET and that the impact of side effects on daily life is fairly limited for most patients. This has recently also been shown in a study of multiple myeloma (21). Interferon-α is often an option for younger patients with PV and ET with a long life expectancy and often an indolent course of the disease. It is thus particularly important that the treatment does not significantly reduce quality of life. However, it is somewhat disappointing that there was no measurable decrease in reported symptoms that seem to be related to the disease, during the treatment with interferon-α.

ACKNOWLEDGEMENTS

We express our gratitude to Joacim Larsen and Hanna Svensson for help with the statistical analysis.

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