

Assessment of quality of life in patients with chronic myeloid leukaemia on diagnosis and after treatment with imatinib*

Ocena jakości życia pacjentów z przewlekłą białaczką szpikową w chwili ustalenia rozpoznania i po leczeniu imatinibem

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ABSTRACT

Introduction: The aim of the study was to assess the quality of life (QL) in patients with chronic myeloid leukaemia (CML) on diagnosis, and after 1 month and 12 months of treatment with imatinib, and to identify therapeutic elements which significantly lower the QL in the patients.

Materials and methods: Assessment of QL was performed in adult patients diagnosed with CML hospitalized in the Department of Haematology, Department of Chemotherapy, and the Haematology Outpatient Clinic, Pomeranian Medical University in Szczecin (Poland). Quality of life was assessed with 2 questionnaires: EORTC QLQ-C30 and EQ-5D, while symptoms of depression were measured using the CES-D questionnaire. Quality of life was analyzed at 3 time points: on diagnosis (A1), after 1 month (A2), and after 12 months of therapy (A3). All groups of patients were treated with imatinib.

Results: Emotional functioning and global health status and subjective QL significantly improved from A1 to A3. Patients reported significantly less fatigue and pain. Symptoms of depression significantly reduced during treatment. The group of patients caring for others in serious illness had reported a higher index of depression. Patients without any academic degree or extra qualifications, and the group of patients caring for others in serious illness, had reported significantly lower cognitive functioning.

Conclusions: Measurement of various aspects of QL using the EORTC QLQ-C30 and EQ-5D questionnaires showed significant improvements after the 1st month of treatment compared to the state at diagnosis of CML. Due to high levels on the CES-D Depression Scale patients with CML do require constant psychological assistance and in some cases also psychiatric help.

Keywords: chronic myeloid leukaemia; quality of life; depression, imatinib.

ABSTRAKT

Wstęp: Celem pracy była ocena jakości życia (JŻ) pacjentów z przewlekłą białaczką szpikową (PBSz) w chwili ustalenia rozpoznania, po 1 miesiącu i 12 miesiącach leczenia imatinibem oraz próba wybrania z postępowania terapeutycznego elementów, które w sposób istotny wpływają na obniżenie JŻ pacjentów.

Materiały i metody: Ocena JŻ była przeprowadzona wśród dorosłych pacjentów z ustalonym rozpoznaniem PBSz hospitalizowanych w Klinice Hematologii, na Oddziale Diennej Chemioterapii i Poradni Hematologicznej Pomorskiej Akademii Medycznej w Szczecinie, obecnie Pomorskiego Uniwersytetu Medycznego w Szczecinie (Polska). Do oceny JŻ były wykorzystane 2 kwestionariusze: EORTC QLQ-C30 oraz EQ-5D, natomiast do oceny objawów depresji wykorzystano kwestionariusz CES-D. Analizy JŻ dokonano w 3 przedziałach czasowych: w chwili ustalenia rozpoznania (A1), po 1 miesiącu leczenia (A2) oraz po 12 miesiącach leczenia (A3). Wszyscy pacjenci byli leczeni imatinibem.

Wyniki: Funkcjonowanie emocjonalne i JŻ oraz ogólny stan zdrowia uległy istotnej poprawie od A1 do A3. Pacjenci mówili o istotnym zmniejszeniu objawów dotyczących zmęczenia i dolegliwości bólowych. Objawy depresji znamienne zmniejszyły się w trakcie leczenia. Grupa pacjentów cierpiąca na inne poważne choroby odnotowała wyższy wskaźnik objawów depresji. Chorzy nieposiadający stopnia naukowego i innych dodatkowych kwalifikacji oraz pacjenci cierpiący na inne poważne choroby znamienne gorzej ocenili funkcjonowanie poznawcze.

Wnioski: Na podstawie pomiaru różnych aspektów JŻ z wykorzystaniem kwestionariusza EORTC QLQ-C30 oraz EQ-5D wykazano istotną poprawę już po 1. miesiącu leczenia w porównaniu ze stanem przy rozpoznaniu PBSz. Ze względu na wysoki wskaźnik depresji CES-D pacjenci z PBSz wymagają stałej opieki psychologicznej, a w niektórych przypadkach także psychiatrycznej.

Słowa kluczowe: przewlekła białaczka szpikowa; jakość życia; depresja; imatinib.

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INTRODUCTION

The issue of quality of life (QL) in patients, including those with cancer, has been recognized relatively recently, but has already become an important element of planning and qualifying treatment. Quality of life has become an essential criterion for evaluating the effects of therapy in clinical trials, and patient-reported evaluations are essential for the determination of the total efficacy of treatments and for designing new clinical strategies [1, 2, 3]. Interest in this aspect of health care has been and is still highest in the USA and Western Europe, which can be seen in the dramatic increase in the number of published articles in this area over the past 30 years, from 32 in 1973 to over 5,000 in 2004 [4]. However, we found more than 20 papers on the QL of patients with chronic myeloid leukaemia (CML), about 16 of which were published in the last 4 years [5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25], but none from Poland.

Chronic myeloid leukaemia is a systemic disease, but its course is milder than that of acute leukaemias. In some patients the disease is recognized incidentally during control tests, while in others it is from diagnosing symptoms: fatigue, symptoms associated with high leukocytosis, discomfort in the abdomen caused by hepatosplenomegaly, and also immunodeficiency and haemorrhagic diathesis. There is an additional problem associated with diagnosis, treatment of neoplasm and prolonged hospitalization [26].

The aim of treatment of CML is total remission, or the longest possible life of the patient. Until recently, transplantation of bone marrow has been deemed the only certain method of dealing with CML [20, 27]. Only a small number of patients have been able to receive transplants, with the treatment of other patients being based on hydroxyurea or interferon alpha. Treatment with interferon alpha is associated with a negative effect on patient QL caused by physical toxicities, with symptoms such as fever, chills, flu-like symptoms, fatigue, as well as depression, impaired memory and inability to concentrate. Hydroxyurea-based treatment is well tolerated and has few side effects compared with interferon alpha, but is of limited efficacy, with no effect on disease progression or survival [18]. The most recent breakthrough in conservative therapy is an oral targeted therapy with tyrosine kinase inhibitor [1, 2, 7, 8, 9, 17, 18]. The results of IRIS (International Randomized Study of Interferon and STI571) research comparing the treatment with interferon alpha with cytarabine or imatinib resulted in the first targeted therapy with imatinib becoming the standard of first line treatment for CML. The high efficacy of imatinib in CML patients is also accompanied by lower toxicity, which may result in higher assessment of patient QL [1, 18].

The main objective of this study was:

- a) to assess QL in patients with CML on diagnosis (A1), after 1 month (A2), and after 12 months of treatment with imatinib (A3),
- b) to select the therapeutic elements which significantly lowered patient QL.

MATERIALS AND METHODS

Materials

The assessment of QL was performed in adult patients with diagnosed CML hospitalized in the Department of Haematology, Department of Chemotherapy, and the Haematology Outpatient Clinic of the Pomeranian Medical University in Szczecin – PMU (in Poland) between November 2006 and December 2009. The study recruited 48 patients (23 men, 25 women). The mean age of the patients was 57 years (range = 21–88). All patients with CML were treated with imatinib. Before recruitment for the treatment with imatinib the majority of patients (43) received hydroxyurea, 4 patients were treated with low dose of cytarabine and leukapheresis (to reduce leukocytosis). The time from diagnosis to start of the treatment with imatinib was about 2–4 weeks. The inclusion criteria were: age 18 years or more, a confirmed diagnosis of Philadelphia chromosome positive CML and ECOG performance status 0–1. The exclusion criteria were as follows: myeloproliferative neoplasm Philadelphia negative (Ph) negative (–), acute lymphoblastic leukaemia Ph positive (+), other neoplasms and cognitive impairment hampering self-reported evaluation.

The study was approved by the Bioethics Committee of the PMU (BN-001/141/06).

Design of the study and methods

Quality of life was assessed at 3 time points: on diagnosis (A1), after 1 month (A2), and after 12 months of treatment (A3). Quality of life was analyzed with 2 questionnaires: EORTC QLQ-C30 and EQ-5D. Depression was measured using the CES-D questionnaire. Patients completed the questionnaires by themselves or with the help of the author of this paper.

Questionnaire QLQ-C30

The European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire version 3 was developed to assess the QL of cancer patients. QLQ-C30 contains 30 questions, 24 of which form 9 multi-item scales representing various aspects or dimensions of health-related QL: 1 global scale, 5 functional scales (physical, role, emotional, cognitive and social), and 3 symptom scales (fatigue, pain, and nausea). The remaining 6 items are intended to be mono-item scales describing relevant cancer-oriented symptoms (dyspnoea, insomnia, appetite, constipation, diarrhoea, financial difficulties). Responses to the QLQ-C30 are rated on a 4-point scale, from 0, not at all to 4, very much, and 2 questions assessed QL and health from 1–7. The time frame of observation was the previous week [28, 29, 30, 31, 32, 33].

Questionnaire EQ-5D

The EuroQoL-5D (EQ-5D) is divided into 3 sections. The EQ-5D questionnaire has 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) and one overall rating of current health. The 5 EQ-5D dimensions comprise 3 levels, with scores ranging from 1–3. The EQ-VAS section looks like a thermometer, with endpoints of 100 (best

imaginable health state) at the top and 0 (worst imaginable health state) at the bottom. The EQ-5D index is composed of 9 questions, including socio-demographic characteristics of patients [34].

Questionnaire CES-D

The Centre for Epidemiological Studies-Depression Scale (CES-D) is a 20-item self-report scale developed for the general population to measure depressive symptoms during the past week [35, 36]. Responses to the CES-D are rated on a 4-point scale (from 0–3 points, excluding question numbers: 4, 8, 12, 16, which receive reverse scores from 3 to 0 points), and the instrument total score ranges from a minimum score of 0 to a maximum score of 60. Higher scores on the CES-D indicate a greater risk of depression, with scores greater than or equal to 16 indicating the possibility of an increased risk of clinical depression [37].

Statistical methods

Statistical analyses were conducted using Statistica version 9.0 (StatSoft Inc. USA). Individual components of QL and symptoms of depression (only independent measurable variables) were compared against three time intervals (A1, A2, A3) with the Wilcoxon matched pairs test. The test was used when the distribution deviated from a normal distribution in the examined groups. In the analysis of quantifiable variables we used χ^2 tests, and for smaller groups a Yates correction or Fisher exact test. In the analysis of the factors affecting measurable values we used the multivariate analysis of variance in the MANOVA module. Dependences were considered to be statistically significant at $p < 0.05$.

RESULTS

Socio-demographic characteristics of patients with chronic myeloid leukaemia

Analysis of the socio-demographic data (EQ-5D index) showed that 23 (48%) patients had experienced serious illness (other disease than CML), 31 (64.5%) patients had experienced serious illness in their family, and 21 (44%) patients had experienced illness in caring for others. 21 (44%) patients were smokers, with 12 (37.5%) currently smoking. The majority of patients (40 patients; 83%) had secondary or higher education, with 12 of these (37.5%) having academic degree or extra qualifications. A main activity was declared by 24 patients (50%), and 2 patients (4%) worked in health care or social services. The majority of patients were in the chronic phase of CML (46 patients) and 2 patients in the accelerated phase of CML (Table 1).

Quality of life assessment in patients with chronic myeloid leukaemia – EORTC QLQ-C30 questionnaire

EORTC QLQ-C30 Functional Scales

For patients with CML, no significant changes were found in physical and role functioning across the period of treatment. Emotional functioning significantly improved from the 1st diagnosis (A1) to 12 months of treatment (A3; $p < 0.009$). However,

TABLE 1. Socio-demographic characteristics of patients with chronic myeloid leukaemia (CML)

Variable	Patients (n = 48)	%
Sex		
Male	23	48.0
Female	25	52.0
ECOG PS		
0	34	71.0
1	14	29.0
2–4	0	0
Phase of CML		
Chronic	46	96.0
Accelerated	2	4.0
Blast	0	0
Treatment before imatinib		
Hydroxyurea	43	90.0
Cytarabine, Leukapheresis	4	8.0
Serious illness in you yourself		
Yes	23	48.0
No	25	52.0
Serious illness in your family		
Yes	31	64.5
No	17	35.5
Serious illness in caring for others		
Yes	21	44.0
No	27	56.0
Smoker		
Yes	21	44.0
No	27	56.0
Current smoker		
Yes	12	37.5
No	36	62.5
Education		
Elementary	8	17.0
Secondary or higher	40	83.0
Academic degree or extra qualifications		
Yes	12	37.5
No	36	62.5
Main activity		
Retired	21	44.0
Business firm	12	25.0
Keeping house	5	10.5
Employed	5	10.5
Disability pension	1	2.0
Student	2	4.0
Seeking work	2	4.0
Work in health care or social services		
Yes	2	4.0
No	46	96.0

cognitive and social functioning were not uniformly influenced by the treatment. Global health status and subjective QL improved at 1 month (A2; $p < 0.0003$), and 12 months of treatment (A3; $p < 0.001$), compared with that at diagnosis (A1) – Table 2.

EORTC QLQ-C30 Symptom Scales

After 1 month of imatinib therapy (A2) patients reported significantly less fatigue ($p < 0.007$). However, the changes were not significant for nausea/vomiting, dyspnoea, appetite loss, insomnia, diarrhoea, constipation and financial difficulties. Patients noticed less pain at one month (A2; $p < 0.009$) and 12 months after treatment (A3; $p < 0.003$) than at diagnosis (A1) – Table 2.

TABLE 2. Quality of life (QL) assessment in patients with chronic myeloid leukaemia – EORTC QLQ-C30 questionnaire

Symptoms/subscales	Mean (SD)			Wilcoxon test p		
	A1	A2	A3	A1/A2	A1/A3	A2/A3
Physical functioning	8.24 (3.04)	8.00 (2.64)	8.12 (2.95)	NS	NS	NS
Role functioning	2.82 (1.27)	2.92 (1.20)	2.94 (1.37)	NS	NS	NS
Emotional functioning	7.74 (2.65)	7.16 (2.43)	7.50 (2.71)	p < 0.009	NS	NS
Cognitive functioning	3.58 (1.62)	3.58 (1.45)	3.56 (1.45)	NS	NS	NS
Social functioning	3.48 (1.48)	3.40 (1.56)	3.48 (1.59)	NS	NS	NS
Global QL	9.06 (2.74)	9.94 (2.51)	9.86 (2.80)	p < 0.00003	p < 0.001	NS
Fatigue	5.90 (2.34)	5.54 (2.17)	5.70 (2.25)	p < 0.007	NS	NS
Nausea/Vomiting	2.54 (0.90)	2.38 (0.75)	2.56 (0.95)	NS	NS	NS
Pain	3.50 (1.70)	3.20 (1.45)	3.14 (1.44)	p < 0.009	p < 0.003	NS
Dyspnoea	1.42 (0.73)	1.36 (0.59)	1.48 (0.76)	NS	NS	NS
Insomnia	2.06 (1.01)	1.98 (0.86)	1.96 (0.85)	NS	NS	NS
Appetite loss	1.66 (0.71)	1.98 (0.86)	1.66 (0.68)	NS	NS	NS
Constipation	1.54 (0.76)	1.50 (0.67)	1.48 (0.67)	NS	NS	NS
Diarrhoea	1.30 (0.50)	1.32 (0.58)	1.34 (0.59)	NS	NS	NS
Financial difficulties	1.80 (0.85)	1.86 (0.92)	1.90 (0.95)	NS	NS	NS

TABLE 3. Quality of life (QL) and depression assessment in patients with chronic myeloid leukaemia – EQ-5D and CES-D questionnaires

Symptom/subscales	Mean (SD)			Wilcoxon test p		
	A1	A2	A3	A1/A2	A1/A3	A2/A3
Mobility	1.34 (0.51)	1.30 (0.46)	1.28 (0.45)	NS	NS	NS
Self-care	1.02 (0.21)	1.06 (0.23)	1.06 (0.23)	NS	NS	NS
Usual activities	1.22 (0.41)	1.26 (0.23)	1.28 (0.45)	NS	NS	NS
Pain/Discomfort	1.54 (0.52)	1.52 (0.54)	1.50 (0.54)	NS	NS	NS
Anxiety/Depression	1.54 (0.54)	1.54 (0.50)	1.56 (0.50)	NS	NS	NS
Global QL	61.10 (18.63)	67.50 (17.20)	67.00 (19.05)	p < 0.00003	p < 0.0001	NS
CES-D	18.44 (6.58)	17.44 (6.49)	17.38 (6.09)	p < 0.004	p < 0.01	NS

Quality of life assessment of patients with chronic myeloid leukaemia – EQ-5D questionnaire

Patients with CML reported no significant changes in the dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. However, assessment of QL significantly improved at 1 month (A2; p < 0.00003), and 12 months of treatment (A3) compared with that at diagnosis (A1; p < 0.0001) – Table 3.

Depression symptom analysis of patients with chronic myeloid leukaemia – CES-D questionnaire

Symptoms of depression were significantly reduced at 1 month (A2; p < 0.004) and at 12 months after treatment (A3; p < 0.01) compared with that at diagnosis (A1). The CES-D scores during treatment were greater than 16 at the 3 time points, which would indicate the possibility of a greater risk of clinical depression (Table 3).

Quality of life analysis and socio-demographic variables

Based on questionnaire QLQ-C30, it was ascertained that patients with CML that did not have any academic degree or extra qualifications (p = 0.01) and were caring for others with a serious illness (p = 0.005) had significantly worse cognitive functioning. Patients caring for a person with a serious

disease reported higher depression scores (p = 0.02). Other socio-demographic variables had no relation to the level of individual scores (Table 4).

DISCUSSION

Most papers on the assessment of patient from this research were written in the previous 4 years [1, 2, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 22, 24, 25]. Our study is the 1st report that assesses QL in patients with CML in Poland.

The results of our study show no significant changes in physical, cognitive, social and role functioning, mobility, self-care, usual activities and anxiety/depression over the period of treatment. Significant improvements were observed for emotional functioning, global health status and subjective QL. In the symptom scales we noticed a marked reduction in fatigue, pain and symptoms of depression. However, we found no significant differences in nausea/vomiting, dyspnoea, insomnia, appetite loss, diarrhoea and financial difficulties. These findings are partially consistent with Aziz et al. and Molnár et al., who assessed QL in patients with CML treated with tyrosine kinase inhibitor – imatinib [5, 21]. Both those studies used the FACT-BRM questionnaire and showed an improvement in general health

TABLE 4. Quality of life assessment in patients with chronic myeloid leukaemia depends on socio-demographic data – QLQ-C30 and EQ-5D questionnaires

No	Subscales		A1	A2	A3	p	
EORTC QLQ-C30							
1.	Cognitive functioning	in caring for others	no	3.21	3.21	3.35	0.005
			yes	4.04	4.04	3.81	
			p	NS	0.04	NS	
	academic degree		no	3.78	3.67	3.59	0.01
			yes	3.00	3.30	3.46	
			p	NS	NS	NS	
CES-D questionnaire							
2.	Depression	in caring for others	no	16.92	15.5	15.28	0.02
			yes	20.36	19.9	20.04	
			p	NS	0.01	0.004	

and an increase in TOI (Trial Outcome Index), improved emotional functioning, less fatigue, and a reduction of side effects. In contrast to our findings, there were no significant differences in physical, emotional and cognitive functioning. Similar results were noted by Hahn et al., who compared QL in patients with CML treated with imatinib versus interferon alpha [18]. In addition, they also showed in their research that patients who received imatinib compared with interferon alpha plus cytarabine reported higher QL. Findings similar to our paper were also reported by Curran et al. and Efficace et al., who compared the QL in patients with CML treated with imatinib versus interferon alpha with cytarabine [6, 7]. Another study reported by Jain et al. also showed better profile of imatinib compared to hydroxyurea, with significant statistical differences in terms of efficacy, non-haematological toxicity and QL in CML patients [13].

An improvement in the QL of patients with CML treated with another tyrosine kinase inhibitor (TKI) – bosutinib, was shown by Trask et al. based on the FACT-Leu questionnaire, which is consistent with our results [24]. Efficace et al. showed that QL was especially compromised by chronic fatigue, similar to our findings [8]. Slightly different results were obtained by Stalfelt and Zettervall, who observed a deterioration of patient QL in CML during treatment, although the differences were not statistically significant [23]. Differences between Stalfelt and Zettervall and our results can be explained by the different method of treatment. Those patients were subjected to intense chemotherapy, which is associated with long hospitalization and numerous complications related to the administration of cytostatics [23].

Deterioration in patient QL, mainly physical functioning, was also observed by Kiss et al. in CML patients subjected to bone marrow transplantation. Bone marrow transplantation is known to be a procedure associated with high toxicity, many side effects and prolonged stays in hospital, which may have a very adverse effect on patient wellbeing [20]. During such a period patients generally experience a series of somatic, psychological and social side effects [27]. Similar to our results, in a study by Homewood et al. QL in patients treated with interferon alpha [19] was lower in the domains of emotional,

cognitive and social functioning, accompanied by increased fatigue, pain, dyspnoea, nausea and vomiting. It is known that treatment with interferon alpha is associated with physical toxicities, producing symptoms such as fever, chills, flu-like symptoms, hypotension, fatigue, as well as depression, impaired memory and an inability to concentrate [18].

The importance of QL was confirmed by the study of Cella et al. This analysis described TKs therapy-related symptom burden and its effect on adherence and treatment response, outline instruments to measure symptom burden and QL in CML, and summarized the available clinical data on QL of patients on TKI therapy. Quality of life is an aspect of CML disease management that will continue to gain prominence in the coming years [12].

Analysis of factors significantly affecting QL in CML showed that patients with no scientific degree or extra qualifications reported significantly worse cognitive functioning. This finding is not consistent with Hahn et al., where the education level of patients did not have a significant effect on the self-reported QL [18]. On the other hand, Aziz et al. showed that sex, age and Sokal score had no significant relation to QL, which is consistent with our results [5].

Slightly different results were obtained by Efficace et al., who analyzed the effect of age and sex on the QL in patients with CML treated with imatinib. The greatest reduction in role, physical and emotional functioning was reported by young patients and women, while patients above 60 had results similar to the general population, which is inconsistent with our results [7].

The issue of patient QL is mainly studied by researchers in Western Europe and the USA. In Central and Eastern Europe this is rather neglected in the treatment of patients with haematological disorders. Multivariate analysis of the QL in patients with malignant diseases of the blood shows the most relevant aspects concerning not only treatment but the psychological well-being of patients. This information may help improve the model of care, alleviate serious problems for patients through education, advice and support, and may also be important in the selection and possible modification of treatment. This study confirms the need for deeper analysis in this area.

CONCLUSIONS

1. Measurement of various aspects of QL using the EORTC QLQ-C30 and EQ-5D questionnaires showed significant improvements after the first month of treatment (A2) compared to the state at diagnosis of CML (A1).

2. Due to the overall high level of patient depression on the CES-D scale, patients with CML require constant psychological care and in some cases also psychiatric assistance.

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