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REVIEW ARTICLE

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Quality of life of patients with advanced pancreatic cancer

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ABSTRACT

Pancreatic cancer is one of the most common malignancies with poor prognosis and high mortality. Advanced-stage disease at diagnosis and the dominant clinical symptoms significantly deteriorate the quality of life. The paper presents an analysis of the results of quality of life studies in patients with locally advanced and metastatic pancreatic cancer, as well as the relationship between therapeutic decisions and quality of life indicators. It has been shown that the initial assessment of life quality can have prognostic value. Appropriate symptomatic treatment of patients with advanced pancreatic cancer improves the quality of life, increases the compliance and prolongs survival. The assessment of the quality of life in patients with advanced pancreatic cancer has multivariable significance, which is not limited only to improving the quality of life.

Key words: health-related quality of life, advanced pancreatic cancer

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Introduction

The incidence of pancreatic cancer is systematically increasing and since the 1950s it has increased almost 3-fold [1]. Currently, it is the 10th most common neoplasm in both sexes in Europe as well as in the United States [1–3]. The fact that death due to pancreatic cancer is the 4th most common cause of death due to a neoplasm in the world is particularly worrying. The discrepancy between the two classifications is mainly due to the fact that in most patients this cancer is diagnosed in an advanced stage, resulting in poor prognosis. The ratio of mortality to morbidity in pancreatic cancer is 98%, and each year about 40,000 patients die due to this disease [1]. Projections indicate a further increase in incidence and assume that in 2030 pancreatic cancer will be the second most common cause of cancer-related deaths [4, 5].

In Poland, pancreatic cancer is the 11th most common neoplasm in men and the 14th in women. Currently in our country pancreatic cancer is diagnosed in about 3,500 patients per year [6]. Men are affected slightly more often and the peak of the incidence is noted in the range of 65–69 years. In terms of the number of deaths pancreatic cancer ranks the 6th in men (4.4%) and the 5th in women (5.4%) [6]. Deaths are in general noted in the same age group.

Pancreatic cancer is general diagnosed in the advanced stage. Early pancreatic cancer is asymptomatic or oligosymptomatic [7, 8]. The clinical picture of locally advanced or generalized disease is dominated by pain and progressive cachexia, fatigue and insomnia [4, 9]. These symptoms have a significant impact on the quality of life (QoL) and its deterioration is frequently observed already at diagnosis. Survival in this group of patients is short, median overall survival (OS) in the locally advanced stage does not exceed one year, and in generalized cases, it is 3–6 months [2, 10].

Early stage pancreatic cancer is diagnosed in only 10% of patients [11]. Radical treatment is possible only in this group. Surgical treatment (excision of the head of the pancreas with the duodenum, partial peripheral excision of the pancreas or complete excision of the pancreas and the duodenum) [3, 12]. Unfortunately, 80% of operated patients relapse within 2 years (most com-

monly because of metastases) is the standard procedure in this case [2]. In order to improve the results, surgical treatment is combined with adjuvant chemotherapy or radiotherapy.

In the treatment of patients with advanced pancreatic cancer chemotherapy is used as monotherapy or multidrug regimens, most commonly based on gemcitabine, fluoropyrimidine, nab-paclitaxel or irinotecan. However, the effectiveness of this treatment is limited, and the 5-year survival rate still does not exceed 5% [9, 13]. Because of clinical characteristics of pancreatic cancer, limited therapeutic options and poor prognosis, the assessment of the quality of life of the patients is of particular importance.

The aim of this analysis is to present the available quality of life outcomes in patients with locally advanced and metastatic pancreatic cancer and the particular role of quality of life in making therapeutic decisions in this group of patients.

The importance and methods of evaluating the quality of life in cancer patients

According to the position of the World Health Organization (WHO), quality of life (QoL) defines the individual perception of a person's life situation in the context of specific standards and values system in which he/she is living and in relation to his/her achievements, expectations and interests. In medicine QoL is considered as health-related (HRQoL) [14, 15]. This is a narrower topic than QoL in general, but in practice, HRQoL is replaced by QoL.

Quality of life is a method of multidimensional evaluation of patients' well-being and functioning in different areas — physical activities, emotions, social roles, mental health, the socio-economic situation and sexual life. A high value of the HRQoL index indicates that — in spite of the disease — the patient perceives himself as a well-functioning person; a low HRQoL value is a reflection of the limitations that the patient feels. Quality of life is important in clinical trials, where it is a very useful tool for evaluating the value of medical procedures in relation to treatment outcomes and survival of cancer patients [16]. It facilitates planning and organizing extemporary and long-term care, stratification of death risk or of additional hospitalizations which is of particular importance in the case of chronic diseases.

Methods of evaluation used in clinical trials are highly diverse, which often makes interpretation of the results difficult. This phenomenon is based on the fact that QoL is important and meaningful for patients, but it can be difficult to express in methodological categories. Until the 1980s QoL was evaluated in only 5% of clinical trials. In 1981 the European Organization for Research and Treatment of Cancer (EORTC) established the Quality of Life Group, which aim among others was to elaborate multidimensional instruments for evaluating QoL and standardizing of questionnaires. The basic questionnaire elaborated by the group (quality of life questionnaire C-30, QLQ-C30) is one of the most important tools in oncology [17]. It is a validated tool elaborated for cancer patients and intended for prospective analyses, which based on responses to 30 defined questions evaluates 5 domains of activity: physical, emotional, social, cognitive and intensity of symptoms (pain, fatigue, loss of appetite, nausea/vomiting, diarrhea, constipation, sleep disturbances) as well as total QoL. Full assessment in this questionnaire allows to obtaining score values in the range of 0–100, with more points indicating better functioning and less severe symptoms [18, 19].

The EQ-5D questionnaire (Euro QoL) is a tool used for the evaluation of the general health condition [20]. It contains 5 closed questions concerning the physical and mental functioning sphere (ability to move, self-care, daily activities, pain/discomfort and anxiety/depression). It allows to compare the quality of life of patients with the population norm. Thanks of this methodology, it is a tool recommended among others by NICE (National Institute for Care Excellence) for pharmacoeconomic evaluation, even though it is simpler than the EORTC scale

The evaluation of the quality of life has become an indispensable element in phase III clinical trials in oncology. The 2013 Cancer Research Committee of the American Society of Clinical Oncology (ASCO) guidelines for the evaluation of the results of clinical trials with anti-cancer drugs indicated a significant improvement in the quality of life — in addition to an improvement in overall survival — as one of the indicators which determine clinically significant trial results [21]. In 2013 the European Society of Medical Oncology (ESMO) also initiated work on a ESMO Magnitude of Clinical Benefit Scale (ESMO MCBS), in which the determination of QoL is one of the important parameters [22].

Systemic treatment of patients with advanced pancreatic cancer

Chemotherapy is the standard treatment of patients with locally advanced or metastatic pancreatic cancer. The first drug used for this indication was fluorouracil. Its administration allowed for about 10% of objective responses but did not improve QoL and OS [23]. Almost until the end of the 20th century in spite of a number of clinical trials no benefit was shown for multidrug combinations based on fluorouracil [24]. Some pro-

gress was only noted in 1997 when gemcitabine in monotherapy was shown to be superior to fluorouracil. Even though the OS benefit was minimal (the median still did not exceed 6 months), there was an improvement in performance status, better pain control and QoL improvement in patient treated with gemcitabine [25]. Gemcitabine became the standard of care in this indication for many years. In further phase III studies the combination of gemcitabine with a number of drugs with different mechanisms of action (e.g. capecitabine, irinotecan, oxaliplatin, vismodegib, sorafenib, masitinib) was investigated, but no significant improvement in OS was shown. The exception was a trial performed in 569 patients with unresectable, locally advanced or metastatic pancreatic cancer, in which erlotinib used in combination with gemcitabine significantly improved the outcomes — however, the median OS was only prolonged by 2 weeks (6.24 *vs.* 5.91 months, hazard ratio [HR] 0.82; P = 0.038), and progression-free survival (PFS) by a few days (3.75 *vs.* 3.55 months, HR 0.77; P = 0.004). The objective response rates (8.6% *vs.* 8%) and disease control rates (57.5% *vs.* 49.2%; P = 0.07) were comparable. Combined therapy led to increased toxicity, although it had no major impact on QoL [25]. The years 2000–2010 are therefore called a decade of failures.

For many years, the use of multidrug regimens in patients with metastatic pancreatic cancer was the subject of controversy. Progress has been made only in recent years when the results of two phase III trials were published showing a significant and clinically relevant benefit of the use of multidrug regimens in terms of overall survival.

In the academic PRODIGE 4 phase III trial performed in 342 patients with metastatic pancreatic cancer with a good performance status (0 or 1 in the Eastern Cooperative Oncology Group [ECOG] scale) the combined treatment according to the FOLFIRINOX regimen (oxaliplatin, irinotecan, leucovorin and fluorouracil) was compared with monotherapy with gemcitabine, showing a significant improvement in median PFS (6.4–3.3 months, P < 0.001) and OS (11.1–6.8 months, P < 0.001), albeit at the cost of higher toxicity [26]. Such treatment is currently recommended for patients with good and very good performance status.

In the MPACT phase III trial in 861 patients with metastatic pancreatic cancer, an innovative albumin-bound paclitaxel (nab-P, nab-paclitaxel) combined with gemcitabine was compared with gemcitabine alone. The combination arm showed a significant OS prolongation (8.5 months in comparison with 6.7 months in the group receiving gemcitabine alone) and a 28% reduction in the risk of death (HR 0.72, P < 0.001) [27]. The 12-month survival rate was significantly higher in the group receiving nab-P and gemcitabine (35% in comparison with 22% in the group receiving monotherapy; P = 0.0002). Median PFS in the group receiving combined treatment and gemcitabine alone was 5.5 months and 3.7 months, respectively (HR = 0.69, P = 0.000024), and the objective response rate (ORR) was 23% and 7%, respectively. Moderate toxicity was observed during combined treatment with nab-paclitaxel and gemcitabine with manageable adverse reactions. There have also been some data suggesting the possibility of nab-P dose reduction in the case of toxicity, which allows obtaining optimal treatment results with acceptable toxicity [3]. The combination of nab-paclitaxel with gemcitabine has become the new standard of systemic therapy in patients with advanced or metastatic pancreatic cancer.

Evaluation of quality of life in patients with advanced pancreatic cancer

The evaluation of QoL indices in pancreatic cancer patients was the subject of research as early as the 1990s. The so-far few studies on QoL in patients with pancreatic cancer indicate that it is reduced already at the beginning of the disease, and mental functioning is significantly worse than in patients with other cancers [16]. However, the assessment of QoL in pancreatic cancer patients is extremely difficult due to the nature of the disease, the high burden of morbidity and mortality, treatment complications and predominant clinical symptoms (pain, cachexia, fatigue), which have an additional negative impact on QoL [9]. Older studies had a number of limitations due to the small sample size, lack of a complete patients characteristic and methodology (e.g. using different — often not validated — tools or different criteria of selecting data for analysis and the use of descriptive statistics only, which practically excludes reliable comparison of individual parameters) [16].

The most recent studies use the EORTC-QLQ-C30 and EQ-5D questionnaires. In a study published in 2006, which included only 57 patients with pancreatic cancer on the basis of EQ-5D, a deterioration of QoL in comparison with the population norm was observed from the diagnosis [9]. In men, this deterioration affected all domains whereas in women a clear tendency for anxiety and depression was observed. The evaluation of QoL using the QLQ-C30 EORTC scale confirmed the deterioration of all five areas of the quality of life in men, whereas in women it mainly concerned physical functioning, social roles and cognitive functions [9]. The differences between two sexes in the areas of deteriorated functioning in pancreatic cancer patients are an important observation derived from this analysis; however, it requires further investigations.

In 2013 Guorgou et al. published the first complete analysis evaluating the quality of life of patients with

advanced pancreatic cancer receiving chemotherapy according to the FOLFIRINOX scheme or gemcitabine in the PRODIGE 4 trial [10]. Earlier, limited reports already indicated disorders of the global health status (GHS) and the occurrence of fatigue, pain and deterioration of physical, emotional and social functioning of pancreatic cancer patients receiving chemotherapy according to the FOLFIRINOX regimen [26]. In the trial, the EORTC-QLQ-C30 questionnaire was used which was completed by the patients at baseline (before randomization), and every 2 weeks thereafter until disease progression. Due to frequency of evaluation it was decided that both the percentage of patients completing the questionnaire and the responses obtained would be performed at baseline, after 15 and 30 days and then after 2, 4, 6, 8 and 10 months. At the beginning of the trial, the questionnaire was completed by 95% of patients treated according to the FOLFIRINOX scheme and 92% of patients receiving gemcitabine. During the trial, this percentage gradually decreased and after 10 months it was 40% and 67%, respectively.

The quality of life analysis included 342 patients with advanced pancreatic cancer — 171 patients each in the arm receiving FOLFIRINOX chemotherapy or gemcitabine alone. One of the inclusion criteria was the performance status (PS) of 0–1 in the ECOG scale, which seems understandable in patients receiving multidrug chemotherapy. It is therefore surprising, that 30 patients (1.4%) receiving FOLFIRINOX and 26 patients (16.6%) treated with gemcitabine alone stated during the initial QoL evaluation that they have to stay in bed or an armchair for "quite a lot`" or "a lot" of time. This observation confirms earlier observations of worse QoL in pancreatic cancer patients already at diagnosis. This also indicates the fact frequently described in the literature that QoL evaluation is subjective and variable. The initial QoL evaluation was similar in both arms. It indicated the intensification of symptoms such as anorexia, fatigue, pain, insomnia and constipation, but at the same time, it was high in the scope of the general functioning of the patients. No significant deterioration of QoL was noted during treatment in spite of the increase in diarrhea intensity especially in the group receiving FOLFIRINOX. GHS change during the trial was similar in both arms. In patients receiving FOLFIRINOX chemotherapy a significant improvement in physical functioning was observed ($P < 0.001$), and a significant improvement in emotional functioning was noted in both arms ($P < 0.001$). Moderate deterioration of GHS (≥ 10 points compared to baseline) occurred in 30.1% of patients receiving chemotherapy according to the FOLFIRINOX scheme and 18.5% of patients receiving gemcitabine.

In this analysis, the time until definitive deterioration (TUDD) of GHS and QoL was analyzed. Median TUDD (to deterioration by ≥ 10 points) was significantly longer in the group receiving FOLFIRINOX than in the group treated with gemcitabine in terms of GHS/QoL, all 5 domains of functioning and the severity of 6 main symptoms (fatigue, nausea/vomiting, pain, dyspnea, anorexia, constipation). The statistical significance was maintained for TUDD until deterioration by ≥ 20 points with the exception of emotional functioning and the median was also longer in the arm with combined therapy (not reached for GHS/QoL). A statistically significant correlation was also noted between the improvement of some analyzed parameters and a good treatment response. In the arm receiving FOLFIRINOX chemotherapy, these were GHS, pain and insomnia, whereas in both arms fatigue and dyspnea. Univariate Cox analysis indicated that in both arms particular QoL domains (physical functioning, social roles and severity of such symptoms as fatigue, constipation, dyspnea and anorexia) are significant prognostic factors for OS. After including these parameters in a model encompassing clinical and demographic data the statistical significance was confirmed for physical functioning and the severity of constipation and dyspnea [10].

In conclusion, despite greater toxicity, chemotherapy according to the FOLIRINOX scheme had a favorable effect on QoL, reducing the relative risk of its deterioration by 63% (HR 0.47; 95% Cl: 0.3–0.7; $P < 0.001$). After 6 months a significant deterioration of QoL occurred in 66% patients receiving gemcitabine alone in comparison with 31% receiving the multidrug scheme [26].

In 2016 a systematic review of trials evaluating QoL in pancreatic cancer patients was published [2]. Based on literature review until 2013 a total of 36 papers were found presenting the results of 30 trials, with a median sample size of 311 patients, range (103–832), mainly at the age of 58–66. There was a slight predominance of men (48–65%). The percentage of patients with a metastatic disease varied considerably (31–100%). The HRQoL scores were evaluated in 30 of these trials (comparison of gemcitabine with another drug in monotherapy — 4, comparison of gemcitabine with combination chemotherapy — 22, other treatment regimens — 4), and finally 23 trials were included in the analysis, of which in 19 no significant differences in QoL were found between the therapeutic arms, whereas in 4 (including the previously described PRODIGE 4 trial) differences were observed.

In a Canadian trial comparing the metalloproteinase inhibitor BAY12-9566 with gemcitabine, the superiority of gemcitabine for the evaluated survival parameters (OS, PFS) was demonstrated, including QoL evaluated with use of EORTC QLQ-30 questionnaire. General health status, physical functioning, cognitive functioning, social roles, and degree of fatigue was better in gemcitabine group [28]. In another trial evaluating the

value of metalloproteinase inhibitors in the treatment of pancreatic cancer patients , marimastat was used in combination with gemcitabine [29]. No benefit of this treatment has been demostrated over gemcitabine plus placebo in terms of survival. Quality of life was evaluated on the basis of a specific Functional Assessment of Cancer Therapy — Pancreas (FACT-Pa) questionnaire. By 2 months after treatment initiation there was an improvement in QoL in the gemcitabine/placebo group and a slight decrease in the gemcitabine/marimastat group ($P = 0.048$).

The authors of the cited review also pointed out certain limitations of the methodology used. First of all, the evaluated results most commonly concern patients remaining in the trial at a specific time point in which the QoL analysis was performed and not the entire population. A significant percentage of patients terminate participating in the trial (e.g. because of disease progression or death) and the evaluated population may not be representative, which has also been indicated by the authors of other studies [2, 13].

Pain was assessed in most analyses as a part of univariate analysis and in 7 out of 24 trials a statistically significant difference was demonstrated in the intensity of this symptom between the therapeutic arms. In patients treated with gemcitabine a decrease in pain intensity by 50% was noted and a decrease of the requirement for analgesics by 24%, whereas in the group treated with fluorouracil this was only 5%. Gemcitabine monotherapy was also superior to the metalloproteinase inhibitor BAY12-9566 in terms of pain relief. The results on neoplastic cachexia turned out to be inconclusive and both the severity and the mitigation or stabilization of the level of cachexia were observed.

In a meta-analysis of 91 clinical trials on pancreatic cancer published in 2015 by Carrato et al. [4] only in 5 studies the results of QoL analyses were presented. The small sizes of the analyzed groups and the heterogeneity of this population allowed only to demonstrate a significant decrease in QoL score using various validated EORTC questionnaires, and a higher incidence of anxiety and depression compared to population norm.

An interesting approach to the assessment of QoL in patients with pancreatic cancer was presented in an analysis published in 2018, where for the first time the assessment of the patients' caregivers were included [16]. The authors assumed that such a burdensome and poor prognosis neoplastic disease had an impact on the QoL of caregivers and their relations with patients. A total of 29 studies with qualitative assessment and 7 with quantitative assessment were included in the analysis. In assessment of different QoL domains, a tendency was found to deteriorate the indicators in pancreatic cancer patients compared to healthy people (population norm). Moreover, the results concerning the mental state of patients with pancreatic cancer were worse than in other neoplasms. The studies rarely analyzed in detail the factors contributing to the deterioration of mental functioning, but it was emphasized that unfavorable prognosis, difficult treatment and immunological and endocrine disorders are associated with a particular risk of disturbances in this area. The results of analyses in areas concerning physical and social functioning and overall QoL assessments varied and indicated different burdens and occurrence of symptoms (pain, fatigue or gastrointestinal dysfunction).

In analyses concerning caregivers, the qualitative assessment showed a high degree of negative emotions in caregivers, and quantitative studies found that 14% and 32% of caregivers, respectively, achieve the threshold for clinical depression diagnosis in the relevant questionnaires. Some studies have also found that caregivers are more likely to experience anxiety than patients themselves. The authors concluded that both patients and caregivers experience difficult situations that are important for QoL. At the same time, they indicated the validity of performing routine screening for psychophysical perturbances in patients with neoplastic disease, which is consistent with the position of the American College of Surgeons [16]. In terms of future trials, the authors of that analysis stressed out the need to collect a well-defined group, conduct longer observations with use of reliable statistical methods, and in this context the appropriate size of the analyzed cohort [16].

The first analysis comparing QoL of patients treated with gemcitabine in combination with nab-paclitaxel or gemcitabine in monotherapy was the phase II randomized trial published in 2020 in a group of 125 previously untreated patients with metastatic (102 — 81.6%) or locally advanced (23 — 18.4%) pancreatic cancer [13]. Patients were randomly assigned to both treatments in 1:1 ratio, and all treatment was outpatient. It should be emphasized that in the light of earlier comments on QoL deterioration in pancreatic cancer patients already at diagnosis, patients with factors negatively affecting the physical functioning (i.e. age over 76 years, serious cardiovascular diseases, severe organ failure, disorders which in the opinion of experts increased the risks associated with the therapy, expected survival less than 12 weeks, gastrointestinal dysfunctions, coagulopathies and neuropathy) were excluded. This approach considerably limited the patient population. Finally, the patients in the group receiving nab-paclitaxel with gemcitabine were significantly younger. Sex distribution was similar in both arms. The primary endpoint of the trial was the percentage of patients without deterioration of the QoL after 3 months. The time until definitive deterioration of QoL (TUDD), the time to decrease in the EORTC QLQ-C30 score by at least 10 points were also analyzed and QoL was compared between the arms. As in the

PRODIGE 4 trial the patients completed the EORTC QLQ-C30 questionnaire every 4 weeks, according to EORTC recommendations.

The percentage of patients with no deterioration after 3 months was 34% in the group receiving gemcitabine in monotherapy and 58.3% in the group treated with nab-paclitaxel in combination with gemcitabine (P = 0.018), and after 6 months 27.3% and 36.6%, respectively (P = 0.357). The mean change in score in particular functional domains indicated a statistically significant advantage of combined therapy with the exception of physical functioning, in which the statistical significance was borderline (P = 0.051). In the group receiving gemcitabine alone an increase of all clinical symptoms intensity was observed, except for fatigue, (60.4 *vs.* 5.9, P = 0.027). After 6 months the trend of changes was similar, however, without statistical significance. The median TUDD was 5.36 months in the group receiving combined therapy and 3.68 months in the group treated with gemcitabine alone. The percentage of patients completing the questionnaire was similar in both arms with no significant differences throughout the study, thus did not affect the obtained results.

Summary

Multivariate analyses in cancer patients confirm the prognostic value of physical functioning and the severity of pain and anorexia, and also indicate a relationship between QoL and OS, although there have been no conclusive data for the homogeneous pancreatic cancer patients population.

In the described trials it was demonstrated that combining the initial QoL assessment with demographic and clinical data enables a more accurate evaluation of survival probability, which means that it can be of prognostic value. All studies showing differences in OS between treatment arms showed a parallel improvement in QoL and a reduction in pain intensity.

Appropriate methods of symptomatic treatment (including side effects management) in patients with advanced pancreatic cancer improve their comfort of life, increase the compliance and contribute to longer survival. Monitoring the quality of life and managing the disease symptoms has a positive effect on treatment outcomes.

The high degree of correlation between severity of clinical symptoms and the results of QoL evaluation indicates that the determination of the value of this parameter should be taken into consideration when making clinical decisions.

The above-mentioned observations indicate that QoL evaluation in patients with advanced pancreatic cancer has multidimensional significance and encompasses not only improvement of the patients' comfort but also their survival. It can be also hypothesized that it has an impact on the QoL of caregivers. Therefore, further investigations are necessary in this field, which would evaluate more accurately the quantitative relations between quality of life and demographic and clinical parameters of the analyzed patients, as well as social and interpersonal relations. Particular attention should be focused on proper methodology, the size of the analyzed groups and statistical analysis methods .

Conflict of interest

The authors have no conflict of interest to declare.

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