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Changes in quality of life and symptoms of patients with multiple myeloma, before and after autologous hematopoietic stem cell transplantation

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OBJECTIVE **To assess the quality of life (QoL) and the reported symptoms of patients with multiple myeloma (MM) before and after autologous hematopoietic stem cell transplantation (AHSCT).** METHOD **A prospective and longitudinal study was conducted between September 2015 and December 2016. The study sample consisted of MM patients who were scheduled to undergo AHSCT. The European Organisation for Research and Treatment of Cancer scale was used to assess patients' QoL (EORTC QLQ-C30, version 3.0) and the MD Anderson Symptom Inventory (MDASI) to record patients' symptoms. Patients completed the questionnaires at two time points, before (after the end of the induction treatment) and one month after AHSCT.** RESULTS **The sample consisted of 83 MM patients who underwent AHSCT (response rate: 69.2%). Patients' mean age was 60±4 years and 70% were men. Patients received induction regimens, with the combinations based on international protocols applied in the treatment of MM. Preparation for AHSCT was performed using the alkylating agent melphalan. The quality of life significantly improved after the AHSCT, based on the EORTC QLQ-C30 scale, except for the symptom of diarrhea which remained unchanged (p=1.000). Overall, a statistically significant improvement in both MDASI subscales (p<0.001) was observed after AHSCT. The emotional functioning (p=0.083) subscale of the EORTC QLQ-C30 was associated with gender and social functioning (p=0.037) and pain subscales (p=0.059) were associated with marital status.** CONCLUSIONS **Patients' overall QoL and symptoms improved after AHSCT. This reflects positively on the overall outcome of their chronic disease. There is always a need to systematically evaluate the effects of MM and AHSCT on patients' QoL, in order to adequately meet their needs.**

Αλλαγές στην ποιότητα ζωής και στα συμπτώματα των ασθενών με πολλαπλό μυέλωμα, πριν και μετά από αυτόλογη μεταμόσχευση αιμοποιητικών βλαστοκυττάρων

Περίληψη στο τέλος του άρθρου

Key words

Autologous hematopoietic stem cell transplantation
Multiple myeloma
Patients
Quality of life
Symptoms

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Multiple myeloma (MM) is a plasma cell dyscrasia characterized by the presence of clonal plasma cells in the bone marrow, monoclonal paraprotein in the serum or urine, while in symptomatic patients there is damage to end organs (blood, kidneys, and bones).[1] In most cases, patients present with hypercalcemia, renal failure, anemia, bone pain –collectively known with the acronym CRAB– but the definite diagnosis requires a bone marrow biopsy. Adults of any age can be diagnosed with MM, but it is more frequent in people over 65 years old, and in men rather than women.[2] A total of 35,730 new cases of MM were estimated in the United States of America in 2023, with 12,590 estimated deaths from the disease.[3] In 2015, about 40,000 people were diagnosed with MM in Europe, and this number is predicted to increase to almost 46,000 by the year 2025.[4] European data also show that in Greece, MM incidence was estimated in 7.3 cases per 100,000 inhabitants.[5]

Treatment for MM includes high-dose chemotherapy (HDT) and autologous hematopoietic stem cell transplantation (AHSCT). Patients eligible for AHSCT (<65 years old with good performance status and no severe comorbidities) are typically given a triplet regimen (VRd: bortezomib, lenalidomide, dexamethasone; DRd: daratumumab, lenalidomide, and dexamethasone; KRd: carfilzomib, lenalidomide, and dexamethasone) for 3–4 months prior to stem cell collection in order to reduce tumor cell numbers in the bone marrow. Collected cells can be transplanted early or on a delayed schedule (after 8–12 cycles of the initial therapy or after first relapse).[6–8] Nowadays, with the availability of novel treatments, the overall survival of MM has increased and MM is now a chronic disease. With improving survival, there is also a focus on the long-term complications and the quality of life (QoL) in the survivorship phase.[9]

Quality of life is defined by the World Health Organization (WHO) as *"an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"*.[10] It is a broad concept, influenced in a complex way by physical health, psychological state, level of independence, social relations and reactions to important characteristics of people's environment. The term "QoL" is also referred to as "subjective well-being". The multidimensionality of QoL refers to the coverage of a broad range of content, including physical, functional, emotional, and social well-being.[11]

AHSCT is associated with considerable toxicities and morbidity that severely impacts patients' recovery process and adversely affects their QoL. The transplant itself induces symptom burden and an impairment of patient's QoL, but this is in most cases temporarily. Most patients achieve their prior health status and QoL 1–2 months after AHSCT. Also, AHSCT recipients have improved long-term QoL.[8] Nevertheless, the effects of MM and treatments induce various symptoms and problems that lead to a high percentage of unmet supportive care needs that impact their QoL. Patients with MM often report unmet needs at the informational, physical, emotional, and daily living/practical domains.[12] Therefore, the continuous investigation of this changing supportive care needs and the assessment of QoL throughout the disease trajectory is nowadays essential for healthcare professionals, in order to optimize patient outcomes.

Overall, although side effects associated with anticancer treatments are well reported, in recent years much attention has been given to assessing the QoL of patients with MM after completion of induction regimens and before entering transplantation. This increase in interest leads clinicians to a more holistic and integrative approach in treating patients before and after AHSCT, since they also give attention to psychological and social aspects, not only to physical symptoms. Although innovative drugs have been added to the treatment of MM, intense toxicities continue to occur, which together with megatherapy interfere with the QoL patient with MM. Thus, the purpose of the study was to assess the changes in QoL and symptoms from the disease and treatment of patients with MM before and after AHSCT.

MATERIAL AND METHOD

Design

A prospective and longitudinal study was conducted during the period from September 2015 to December 2016. Patients were asked to complete the study's scales in two time points. Baseline assessment was performed after the end of the cycles of induction treatments, just before the start of the transplant. The second assessment was done at the first follow-up of the patients approximately one month after AHSCT.

Setting

The study was conducted at the Hematopoietic Stem Cell Transplantation Unit of a central and large university hospital in Athens. It is worth mentioning that this unit also treats patients from other departments of the same hospital, as well as from public hospitals and private clinics in the Attica region and other areas of the country.

Sample

The study sample consisted of patients with MM that were scheduled to undergo AHSCT. We included patients who received the alkylating agent melphalan in high doses as an age-matched transplant preparation (myeloablative) regimen. The highest dose of melphalan was up to 200 mg/m^2. Patients who had a reduced ability to communicate and cognitive function were excluded from the study.

During the study period, 120 MM patients underwent transplantation in the transplant unit. Of these, 22 patients declined to participate in the study, while 15 patients did not complete the data collection tools after their transplant. Ultimately, 83 patients were included in the study's sample (response rate: 69.2%).

Measurement scales

The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0 is a self-reported instrument designed to assess the QoL in cancer patients.[13] It consists of 30 questions divided into five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, pain, and nausea/vomiting) and overall health and QoL scale. The questionnaire also presents six single-items, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. The patients assessed their functional level and symptoms severity on a Likert scale (range from 1=not at all to 4=very high) and their global health status/QoL on a Likert scale ranging from 1=very poor to 7=excellent. Scale scores were linearly transformed into a score ranging from 0 to 100. The score is calculated from 0 to 100. For the functional subscales and overall health and QoL, higher scores mean a better level of functionality and QoL. For symptom subscales, a higher score means more severe symptoms.[13] The Cronbach's alpha coefficient for this study was 0.968. The validation of the questionnaire in Greek revealed a valid and reliable tool.[14] The scale had high internal consistency with Cronbach alpha range from 0.702 to 0.988.

The MD Anderson Symptom Inventory (MDASI) is used to assess the presence and severity of cancer-related symptoms experienced by patients with cancer and their impact in daily living, in the last 24 hours. The questionnaire consists of two parts. The core MDASI (part I) consists of 13 symptom items and rated based on their presence and severity. Each symptom is rated on an 11-point numeric scale ranging from 0 (not present) to 10 (as bad as you can imagine). In part II of the questionnaire, patients rate the degree to which symptoms interfere with their daily lives (general activity, mood, work, relations with other people, mobility and enjoyment of life). These range from 0 (did not interfere) to 10 (interfered completely). The Greek version MDASI was translated and validated by Mystakidou et al.[15] In the study, the scale demonstrated excellent internal consistency with Cronbach's alpha values 0.906 for MDASI I and 0.886 for MDASI II.

Ethics

The study was approved by the Hospital Ethics and Research Committee. Patients were approached by the researcher who explained the purposes and needs of participating in the study. As long as patients consented to participate in the study and met the inclusion criteria, they were included in the study. All patients signed an informed consent prior to their participation.

Statistical analysis

Continuous variables values are presented using the number of participants (N), the mean values and the standard deviations (SD). For the categorical variables the frequencies (n) and the corresponding percentages (%) were used. Normality of the measurement distribution was assessed using the Kolmogorov-Smirnov test and the normal probability plot. Longitudinal comparison of questionnaire subcategories between the interventional assessment and the post-transplant assessment was performed using the paired samples t-test or the Wilcoxon test in case the condition of normal distribution of the data was not met. Also, to examine which factors influence the change in QoL after AHSCT, the absolute change of the variables was calculated from pre-transplantation to post-transplantation. The comparisons of pre-transplant absolute values and post-transplant absolute changes of variables were performed using the independent samples t-test. In case the condition of the normal distribution of the data was not met, the non-parametric Mann-Whitney test was used. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS), version 17.00 (SPSS Inc, Chicago, IL). All tests will be two-sided. A p-value <0.05 was defined as the level of statistically significant difference, borderline statistically significant differences (0.05<p<0.1) were also recorded.

RESULTS

Sample characteristics

The average age of the participants was 60 years (37–70 years). Of the total sample, 70% were men and 30% women. Additionally, 86.7% were married, while 13.3% were single.

Quality of life and changes before and after autologous hematopoietic stem cell transplantation

Table 1 shows the longitudinal analysis of the EORTC QLQ-C30 subscales. A statistically significant improvement is observed in the functional subscales and a statistically significant improvement in the symptom subscales, except for diarrhea which remains unchanged (p=1.000).

Symptoms and MD Anderson Symptom Inventory changes before and after autologous hematopoietic stem cell transplantation

Table 2 presents the longitudinal analysis of the items of the MDASI. A statistically significant improvement was observed in all items of the MDASI I subscale, except for diarrhea (p=0.280). There is also a statistically significant improvement in all the items of MDASI II except for the item related to the impact on work and household activities (p=0.546). Overall, a statistically significant improvement in both MDASI subscales (p<0.001) is observed after AHSCT.

Factors affecting the changes in quality of life and reported symptoms

Age, sex, and marital status were not associated with patients' QoL or reported symptoms using the MDASI nor with their changes before and after AHSCT. Table 3 presents only the significant associations. The emotional functioning subscale of the EORTC QLQ-C30 was marginally statistically

Table 1. Longitudinal analysis of the EORTC QLQ-C30 subscales and items.

EORTC QLQ-C30	Before AHSCT	After AHSCT	p-value
	Mean±SD	Mean±SD	
Global health status/QoL	58.33±21.07	86.24±14.04	<0.001
Functional scales (higher score shows better QoL)			
Physical functioning	77.51±15.54	93.09±10.49	<0.001
Role functioning	71.29±16.73	92.17±13.61	<0.001
Emotional functioning	56.12±18.13	80.22±14.59	<0.001
Cognitive functioning	92.37±11.73	98.59±5.34	<0.001
Social functioning	74.10±21.66	94.78±12.19	<0.001
Symptom scales/items (lower score show better QoL)			
Fatigue	28.92±17.52	10.44±13.48	<0.001
Nausea and vomiting	11.85±13.15	1.20±7.71	<0.001
Pain	22.49±21.53	5.42±11.38	<0.001
Dyspnea	19.28±20.90	4.82±11.79	<0.001
Insomnia	37.75±23.73	12.05±18.46	<0.001
Appetite loss	24.50±18.83	4.82±12.89	<0.001
Constipation	34.54±19.09	7.23±14.77	<0.001
Diarrhea	2.01±9.53	2.01±9.53	1.000
Financial difficulties	7.23±18.80	2.41±8.68	0.018

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer, AHSCT: Autologous hematopoietic stem cell transplantation, SD: Standard deviation, QoL: Quality of life

significantly higher in men than in women (p=0.083). After AHSCT, emotional functioning improved more in men than in women. In addition, married patients showed greater improvement in social functioning (p=0.037) and pain (p=0.057) subscales of the EORTC QLQ-C30 compared to single patients.

DISCUSSION

The purpose of the study was to assess the change in QoL and symptoms from the disease and treatment of patients with MM before and after AHSCT. In the present study, patients reported significant improvement in their overall QoL after transplantation. It is noteworthy that the patients showed an improvement in their symptoms and their functionality after the transplant. In addition, the impact of their symptoms on daily life was also a lesser amount. Diarrhea was the only symptom that did not improve significantly one month after transplantation.

The patients' demographics are in agreement with current literature. MM is a disease of older people with the median age at diagnosis being 65–70 years and median age at diagnosis being 69 in the USA.[9] Our sample had a mean age of 60 years±4.7 years. Moreover, the majority of the study's patients were men (70%). Worldwide, MM is one and a half times more frequently diagnosed in men than women. This trend could be attributed to the fact that men are more susceptible to health-risking behaviors, such as smoking, excessive alcohol consumption, lack of exercise and higher rates of obesity. However, this is yet to be scientifically proved.[16]

The conditioning regimen for the AHSCT preparation received by the patients was melphalan in doses up to 200 mg per square meter of patient surface area (m^2), following onset regimens and preceding transplantation. Melphalan is the most widely used preparative regimen for AHSCT for more than 50 years. Its toxicities include bone marrow suppression, oral mucositis, nausea, vomiting, diarrhea, alopecia, transaminitis, and interstitial pneumonitis.[17] Our results indicated that diarrhea was the only symptom that did not improve after AHSCT, as demonstrated in both measurements scales. Diarrhea is one of the main causes of morbidity after high-dose chemotherapy (especially with melphalan), followed by AHSCT. Almost half of patients receiving AHSCT report diarrhea, which results from cumulative factors. These include the effects of the

Table 2. Longitudinal analysis of the MDASI subscales and items.

MDASI	Before AHSCT ±SD	After AHSCT ±SD	p-value
MDASI I			
Pain	1.92±1.87	0.46±0.99	<0.001
Fatigue	1.82±1.67	0.40±0.62	<0.001
Nausea	0.75±0.79	0.14±0.61	<0.001
Disturbed sleep	2.95±2.44	1.13±1.64	<0.001
Distress	3.51±2.62	1.83±2.12	<0.001
Shortness of breath	1.33±2.42	0.08±0.28	<0.001
Memory problems	0.12±0.40	0.00±0.00	0.007
Anorexia	1.06±1.29	0.39±1.20	<0.001
Drowsiness	1.41±2.45	0.19±1.03	<0.001
Dry mouth	1.16±0.16 2,33	0.00±0.45	<0.001
Sadness	3.04±0.92 2,75	0.00±1.35	<0.001
Vomiting	0.80±1.54	0.11±0.70	<0.001
Numbness and tingling	4.55±2.27	2.10±1.60	<0.001
Diarrhea	0.30±0.98	0.16±0.83	0.280
Constipation	2.39±0.40 2,12	0.00±0.80	<0.001
Total	27.08±8.46 19,61	0.00±8.29	<0.001
MDASI II			
General activity	2.72±1.75	1.20±0.85	<0.001
Mood	3.01±2.91	1.51±1.02	<0.001
Work	2.31±2.12	2.22±1.99	0.546
Relations with other people	2.27±1.89	1.88±1.25	<0.001
Walking	2.68±2.36	1.02±0.54	<0.001
Enjoyment of life	2.51±1.88	1.20±1.12	<0.001
Total	16.39±11.35	9.12±4.58	<0.001

MDASI: MD Anderson Symptom Inventory, AHSCT: Autologous hematopoietic stem cell transplantation, SD: Standard deviation

Table 3. Statistically significant changes in EORTC QLQ-C30 subscales before and after transplantation.

EORTC QLQ-C30 subscales	Men	Women	p-value
Emotional functioning	26.58±19.53	18.33±19.84	0.083
	Married	**Single**	
Social functioning	21.99±26.95	12.12±10.78	0.037
Pain	-18.75±20.73	-6.06±18.67	0.059

All values presented as mean±SD

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer, SD: Standard deviation

chemotherapy regimens on the gastrointestinal mucosa, the effects of the broad-spectrum antibiotics for the prophylaxis and treatment of neutropenia and infections and potential viral, bacterial, or parasitic infections.[18,19] Therefore, a careful evaluation and differential diagnosis of patients with diarrhea is needed, as insufficient control can lead to further dehydration, weakness, malnutrition, anorexia, which will significantly delay the patient's recovery after transplantation.

Symptom burden in patients undergoing AHSCT was investigated by Anderson et al,[20] and at the nadir phase (the point of lowest white blood cell count [WBC]) the most severe symptoms reported by patients included lack of appetite, fatigue, weakness (feeling sick), disturbed sleep, nausea and diarrhea. These symptoms had mild intensity that amplified progressively during conditioning and transplantation and peaked at the nadir phase. Also, in the study of Naegele et al,[21] the most frequent, intense and distressing physical symptoms were fatigue, diarrhea and decreased appetite, having a climax on intensity (decreased appetite 2.79) and distress (diarrhea 2.11) during high-dose melphalan and the nadir. Campagnaro et al[22] evaluated the symptom burden before and after AHSCT and they also agreed on the improvement of both physical symptoms (pain) and the improvement of the emotional state (sadness-mood). Based on the systematic review by Nielsen et al,[23] after AHSCT, the largest reported improvement in symptoms was for fatigue. Our finding placed fatigue at a second place of improvements after HSCT and first was the symptom of insomnia (based on the EORTC QLQ-C30 items).

Patients' overall QoL was ±SD=58.33±21.07 before AHSCT and ±SD=86.24±14.04 after AHSCT, indicating a significant improvement approximately one month post AHSCT. Consistent with our findings, various studies with different research designs, such as variations in the evaluation time points post AHSCT, have demonstrated improvements in the overall QoL, symptoms and functionality of MM patients after AHSCT.[8,24–29]

Research has shown that QoL tends to decline during the AHSCT process, but studies also indicate later improvements within the first two months following transplantation.[8,24,25,28,30–32] This finding could be attributed to the protective measures and isolation that the patients are enduring. Patients at the acute phase of AHSCT have limited human contact and visitations that lead to feelings of loneliness, stress and a general psychological distress that worsen their QoL.[33] This is shown at a study where patients who received HDT as an outpatient had significantly higher score for social/family well-being than those who were hospitalized. However, hospitalized patients had a significantly higher physical well-being score when compared to outpatients. While these differences were statistically significant, it is uncertain whether those differences are clinically meaningful and this study does not suggest a benefit in QoL when HDT is performed in an inpatient versus outpatient setting.[32] Clinically meaningful improvements in global QoL, physical functioning and reduction of pain and fatigue are much more expected to happen during primary treatment regimens (like HDT and AHSCT), while relapsed MM patients report no change or even worsening their QoL.[34]

Additionally, married patients had better social functioning and reported less pain. Similarly, in the study of Kang and Choi, married patients with MM demonstrated higher global health status/QOL and symptom QOL, as measured with the EORTC QLQ-C30.[35] Furthermore, an improvement in the emotional functioning subscale of QoL was observed our men patients, after AHSCT. However, this has not been confirmed by other studies.[25,26] Age was not associated with QoL and symptom changes over time. Other studies have shown that younger patients with MM report worse QoL compared to older patients and healthy individuals.[36,37] This could be explained by the more intensive treatment that younger patients receive. However, overall QoL is significantly impaired in both young and older MM patients.[36] Lastly, the MDASI II items related to the impact on work and household activities did not show improvement. This is likely due to the fact that patients had not yet returned to work during this period, and had also not returned to their daily labor activities due to limitations caused by cytopenias.

The present study has certain limitations. The small research sample and the data collection only from one transplant unit limit the generalizability of the results to all MM patients and AHSCT recipients. Additionally, the single assessment of patients one month after transplantation may not be sufficient to capture the ongoing distress they experience during this period.

New therapies and the development of transplantation and new supportive care methods for the management of MM have paid off as patients' survival and QoL have improved significantly. QoL is a major outcome measure for evaluating the impact of anticancer treatments and AHSCT. Due to the fact that QoL is subjective, a deeper investigation with a combination of research methods (quantitative and qualitative) is clearly needed to encompass all of its aspects (physical, psychosocial, spiritual). Additionally, to achieve this, healthcare professionals need to act as a multidisciplinary team, remain aware of QoL issues and address them in a timely and proper manner. The perception of QoL needs to be understood and appreciated by all, serving as a common language of communication among patients, caregivers and healthcare professionals.

ΠΕΡΙΛΗΨΗ

Αλλαγές στην ποιότητα ζωής και στα συμπτώματα των ασθενών με πολλαπλό μυέλωμα, πριν και μετά από αυτόλογη μεταμόσχευση αιμοποιητικών βλαστοκυττάρων

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ΣΚΟΠΟΣ Η αξιολόγηση της ποιότητας ζωής (ΠΖ) και τα αναφερόμενα συμπτώματα ασθενών με πολλαπλό μυέλωμα (ΠΜ) πριν και μετά από αυτόλογη μεταμόσχευση αιμοποιητικών βλαστοκυττάρων (ΑΜΑΚ). **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Μια προοπτική και διαχρονική μελέτη διεξήχθη μεταξύ Σεπτεμβρίου 2015 και Δεκεμβρίου 2016. Το δείγμα της μελέτης αποτέλεσαν ασθενείς με ΠΜ που ήταν προγραμματισμένοι να υποβληθούν σε ΑΜΑΚ. Η κλίμακα European Organisation for Research and Treatment of Cancer χρησιμοποιήθηκε για την αξιολόγηση της ποιότητας ζωής των ασθενών (EORTC QLQ-C30 version 3.0) και το MD Anderson Symptom Inventory (MDASI) για την καταγραφή των συμπτωμάτων των ασθενών. Οι ασθενείς συμπλήρωσαν τα ερωτηματολόγια σε δύο χρονικά σημεία πριν (μετά το τέλος της θεραπείας εισαγωγής) και ένα μήνα μετά την ΑΜΑΚ. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Το δείγμα αποτέλεσαν 83 ασθενείς με ΠΜ που υποβλήθηκαν σε ΑΜΑΚ (ποσοστό ανταπόκρισης: 69,2%). Η μέση ηλικία των ασθενών ήταν τα 60±4 έτη και το 70% ήταν άνδρες.

Η προετοιμασία για ΑΜΑΚ πραγματοποιήθηκε χρησιμοποιώντας τον αλκυλιωτικό παράγοντα μελφαλάνη. Η ΠΖ βελτιώθηκε σημαντικά μετά την ΑΜΑΚ, με βάση την κλίμακα EORTC QLQ-C30 εκτός από το σύμπτωμα της διάρροιας που παρέμεινε αμετάβλητο (p=1,000). Συνολικά, μια στατιστικά σημαντική βελτίωση και στις δύο υποκλίμακες MDASI (p<0,001) παρατηρήθηκε μετά την ΑΜΑΚ. Η υποκλίμακα συναισθηματικής λειτουργίας (p=0,083) του EORTC QLQ-C30 συνδέθηκε με το φύλο και την κοινωνική λειτουργικότητα (p=0,037) και η υποκλίμακα του πόνου (p=0,059) σχετίστηκε με την οικογενειακή κατάσταση. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Η συνολική ΠΖ και τα συμπτώματα των ασθενών βελτιώθηκαν μετά την ΑΜΑΚ, γεγονός που αντανακλά θετικά στη συνολική έκβαση της νόσου τους. Υπάρχει πάντα η ανάγκη να αξιολογούνται συστηματικά οι επιδράσεις του ΠΜ και της ΑΜΑΚ στην ποιότητα ζωής των ασθενών, προκειμένου να καλύπτονται επαρκώς οι ανάγκες τους.

Λέξεις ευρετηρίου: Ασθενείς, Αυτόλογη μεταμόσχευση αιμοποιητικών βλαστοκυττάρων, Ποιότητα ζωής, Πολλαπλό μυέλωμα, Συμπτώματα

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