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Seven – year to 33-year survivals in multiple myeloma

Siedmioletnie do 33-letnie przeżycia w szpiczaku plazmocytowym

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SUMMARY

Out of 600 studied patients with multiple myeloma 88 (14.7%) survived over 7 years including 45 (7.5%) over 10 years, 11 (1.8 %) over 15 years and 7 (1.1%) over 20 years from the disease diagnosis and beginning of antitumor treatment. The patients with long survival were younger (median age 55 years) at the time of diagnosis than the whole studied group and had normal creatinine, calcium and beta$_2$-microglobulin levels in the serum. Sixty eight percent of these patients had stage I or II of clinical progression, 60% had IgG monoclonal protein and 58% had osteolysis. Treatment with melphalan only was given to 18 patients, 30 were treated with melphalan followed by vincristine, cyclophosphamide, BCNU, doxorubicin and prednisone or dexamethasone. Polychemotherapy was given from the time of the diagnosis to 16 patients, 15 received radiotherapy or ^{60}Co irradiation besides chemotherapy and 9 received new agents thalidomide, bortezomib, lenalidomide. In 66% of the evaluated cases the response to treatment was good and in another 34% stabilization of the proliferative process was achieved. The mean duration of the treatment to achieving partial response was 10 months, ranging from 2 to 89 months. The mean duration of good therapeutic response was 70 months. Twelve patients are alive and are being treated, 7 patients remain without treatment. The longest follow up of a still alive patient with multiple myeloma is 31 years after detection of monoclonal protein and 25 years after beginning of antitumor treatment. The longest follow-up of a still alive patient with initially isolated osseous (bone) involvement is 23 years after detection of the first bone lesion and 19 years after generalization of the process. The longest survival of multiple myeloma patient in whom the cause of death was progression of myeloma was 33 years. In 6 cases acute myeloid leukaemia and in 5 cases solid tumors were the causes of death. In 2 patients with myeloid leukemia no plasma cell infiltrates were found at autopsy; it confirms eradication of multiple myeloma.

KEY WORDS: Multiple myeloma – Therapy – Long – term survival

STRESZCZENIE

Spośród poddanych badaniom 600 chorych na szpiczaka plazmocytowego 88 co stanowi 14,7% przeżyło ponad 7 lat w tym 45 (7,5%) ponad 10 lat, 11 (1,8%) ponad 15 lat i 7 (1,1%) ponad 20 lat od rozpoznania choroby i rozpoczęcia leczenia przeciwnowotworowego. Chorych z wieloletnim przeżyciem cechował w czasie rozpoznania choroby niższy wiek (mediana 55 lat) niż w ogólnej populacji z tym rozpoznaniem oraz prawidłowe stężenie kreatyniny, wapnia i beta$_2$-mikroglobuliny w surowicy. Sześćdziesiąt osiem procent chorych wykazywało I lub II okres zaawansowania klinicznego choroby, 60% białko monoklonalne klasy IgG, 58% osteolizę. Osiemnastu chorych leczono wyłącznie melfalanem, 30 melfalanem, a następnie winkrystyną, cyklofosfamidem, BCNU, doksorubicyną i prednisonem lub deksametazonem. Polichemioterapię od rozpoznania choroby zastosowano u 16 chorych, u 15 poza chemioterapią stosowano napromienianie Rtx lub ^{60}Co, a u 9 nowe leki talidomid, bortezomib i lenalidomid. W 66% ocenianych przypadków stwierdzono „dobrą odpowiedź" na leczenie, a u 34% chorych wieloletnia konwencjonalna chemioterapia dawała tylko stabilizację choroby. Czas leczenia do uzyskania częściowej odpowiedzi wynosił średnio 10 miesięcy i wahał się od 2 do 89 miesięcy. Średnia czasu trwania odpowiedzi na leczenie wynosiła 70 miesięcy. Dwunastu chorych nadal żyje i jest leczonych, 7 chorych pozostaje bez leczenia. Najdłuższe przeżycie żyjącej chorej na szpiczaka mnogiego wynosi 31 lat od wykrycia gammapatii monoklonalnej i 25 lat od rozpoznania szpiczaka plazmocytowego. Najdłuższy czas obserwacji żyjącego nadal chorego z pierwotnie odosobnioną postacią kostną szpiczaka wynosi 23 lata od wykrycia ogniska pierwotnego i 19 lat od uogólnienia procesu nowotworowego. Najdłuższy czas

przeżycia chorej na szpiczaka mnogiego, u której przyczyną zgonu była progresja szpiczaka wynosił 33 lata. U 6 chorych przyczyną zgonu była ostra białaczka szpikowa, u 5 nowotwór lity. U 2 chorych z białaczką szpikową w badaniu autopsyjnym nie stwierdzono nacieków plazmocytowych co świadczy o wyleczeniu szpiczaka.
SŁOWA KLUCZOWE: Szpiczak plazmocytowy – Leczenie – Długie przeżycia

INTRODUCTION

The median survival of patients with multiple myeloma was less than one year before introduction of alkylating agents, and the introduction of melphalan in the 1960s resulted in improved survival. More intense chemotherapy regimens increased response rates, but with no improvement in survival compared to melphalan and prednisone [1]. The Myeloma Trialist's Collaborative Group analysed the survival time of 3967 myeloma patients from 27 randomized trials around the world and reported that the median overall survival was 29 months and 19% of patients were alive at 6 years [1]. The proportion of real long-term survivors is small. In reports of a total of > 2500 patients only about 3–4% of patients remained alive after 10 years from the beginning of the primary treatment for multiple myeloma [2–7]. After conventional chemotherapy for multiple myeloma using as first – line treatment melphalan-based anthracycline – free regimens, 13% of 324 patients aged up to 70 years from three prospective Finnish Leukaemia Group trials were alive 10 years after the entry of each individual [8].

Since 1962, research at Department of Hematology of the Institute of Hematology and Transfusion Medicine in Warsaw has been focused on optimisation of treatment methods of patients with multiple myeloma. Studies on conventional chemotherapy efficacy were conducted within the framework of the Ministry of Health program MZ-VIII-2" Blood diseases and Transfusion Medicine", the Government program PR-6 "Controlling neoplasm diseases", "Research and Development Central Program (CBPR –11.5) and the results of these studies were published [9–14]. Long-term survival of multiple myeloma patients treated in our institution was also the subject of earlier publications [15–18]. From very beginning, all patients with multiple myeloma referred to the Institute of Hematology were subjects of investigations during the whole course of their disease which also made possible assessment of longer and longer survivals in an increasing number of patients.

This study reports long-term survival of 600 multiple myeloma patients on conventional chemotherapy with a follow-up of at least 10 years. The study was especially focused on estimation of frequency of long-term survivals in patients with multiple myeloma and finding common clinical and laboratory features present in long-term surviving patients as possible good prognostic factors.

MATERIAL AND METHODS

The survey was carried out on 600 multiple myeloma patients diagnosed before 2000 and treated in the Institute of Hematology and Transfusion Medicine in Warsaw in the years 1962–2009. All patients who had fulfilled the requirement of more than seven year survival from the diagnosis and beginning of treatment for myeloma were included into the study group. The criteria for multiple myeloma diagnosis included: presence of at least 10% of abnormal plasma cells in bone marrow and/or histologic proof of an extramedullary plasmacytoma, presence of monoclonal protein in serum and/or urine or in plasma cell cytoplasm-detected by means of electrophoresis, immunoelectrophoresis, immunofixation and immunofluorescence techniques as well as presence of osteolytic bone lesions in the majority of cases.

Disease staging was performed acc. to the Durie-Salmon system [19] and, also in the majority of cases, acc. to International Staging System [20]. $Beta_2$-microglobulin assessement was possible because we have a serum bank containing samples from myeloma patients since the year 1968. Serum $beta_2$-microglobulin concentration was determined by means of Beckman ARRAY 360 Analyzator. Cytogenetic studies were performed using GTG banding method.

The following criteria of good response (partial response) for treatment were accepted: 50% decrease in bone marrow plasma cell percentage, 50% decrease in serum and/or urine M-component concentration and no progression of bone destruction. The term complete response was defined as complete disappearance of M-protein from the blood and urine, presence of less than 5% plasma cells in the bone marrow, improvement in all of the indirect lesions except bone lesions and persistence of all these findings for over 4 weeks. A near complete response was defined as the absence of monoclonal protein in the serum and urine determined by electrophoresis but with positive immunofixation. The disease was regarded as stable if the M-component did not decrease by 25% but did not either increase during the period of 3 months, nor were there other signs of progression.

RESULTS

Previously reported results of prospective randomised comparative studies on various chemotherapy program efficacy conducted on 322 patients showed that median survival from the onset of antitumour treatment for patients treated from diagnosis with melphalan was 42 months and for those treated according to VMBCP (vincristine, melphalan, BCNU, cyclophosphamide, prednisone) program – 33 months [12]; management by using seguential treatment initially with melphalan and – in case of its inefficacy – according to VMBCP regimen followed by VABCP (vincristine, doxorubicine, BCNU, cyclophosphamide, prednisone) resulted in 47 – month survival [11]. Comparison of efficacy of the alternating treatment acc. to VMCP (vincristine, melphalan, cyclophosphamide, prednisone) and VBAP (vincristine, BCNU, doxorubicine, prednisone) program and treatment acc. to VMCP in 141 poor – prognosis patients (III stage of malignancy, renal failure) revealed that alternating treatment acc. to VMCP/VBAP regimen produced 19 – month – median survival, whereas treatment acc. to VMBCP produced a figure similar to that previously reported – 33 months [13, 14].

Among 600 treated multiple myeloma patients 88 (14.7%) survived more than 7 years from the onset of antitumour treatment including 45 patients (7.5%) with survival duration exceeding 10 years, 11 patients (1.8%) with survival duration exceeding 15 years and 7 patients (1.1%) with survival more than 20 years. More detailed information concerning long-term multiple myeloma survivors is contained in Tables 1–5.

Comparison of the results of studies at the time of diagnosis of multiple myeloma in patients with long survival is presented in Table 1. Compared to general multiple myeloma patient population, long-term survivors were younger and showed normal serum creatinine, calcium and β2M concentration at the time of diagnosis. Sixty patients (68%), were classified as having I or II clinical stage of malignancy and all 55 evaluated patients as having I stage according to International Staging System. In 53 (60%) patients monoclonal protein IgG was detected. In 51 out of 55 evaluated patients serum β2M concentration was below 3.0 mg/l and in 5 evaluated patients no cytogenetic abnormalities were found.

Methods of treatment and response to treatment in multiple myeloma patients with long survival time are presented in Tables 2 and 3. Eighteen patients (20%) received melphalan only, 30 (35%) – melphalan followed by vincristine, cyclophosphamide, BCNU, adriablastine and prednisone (or dexamethasone) according to VMBCP, VABCP, VMCP/VBAP regimens. Since establishing disease diagnosis, 16 patients (18%) were given polychemotherapy and 15 (17%), additionally to chemotherapy, were irradiated by using Rtx or ^{60}Co-therapy. Nine patients (10%) received conventional chemotherapy followed by thalidomide and bortezomib therapy. In 66% of analyzed patients partial response to treatment was observed. Median survival time till achieving partial response was 10 months and ranged from 2 to 89 months. Duration of response to treatment ranged from 6 to 120 months, with the median of 40 months. Duration of proliferative process stabilization ranged from 6 to 240 months, with the mean of 52 months (Table 3).

Table 1. Results of examinations at the time of multiple myeloma diagnosis in patients with long-term survival
Tabela 1. Wyniki badań w chwili rozpoznania szpiczaka plazmocytowego u chorych z długim czasem przeżycia

Parameter	Patients with survival			
	>7 years n=88	>10 years n=45	>15 years n=11	>20 years n=7
Males no. of cases	43	19	4	2
Females no. of cases	45	26	7	5
Age, median (years)	55	52	52	43
Serum creatinine > 2 mg/dl, no. of cases	2 (2.3%)	1	0	0
Serum calcium > 2.75 mmol/l, no. of cases	0	0	0	0
Monoclonal protein isotype, no. of cases				
IgG	53 (60%)	27 (60%)	8 (72%)	4 (57%)
IgA	20	9	1	1
IgM	3	2	0	0
Light chain disease	6	2	1	1
Non-secretory myeloma	6	5	1	1
Stage of disease acc. to Durie and Salmon, no. of cases				
I	32 (36%)	24 (53%)	7 (63%)	5 (71%)
II	28 (32%)	11 (24%)	2 (18%)	0
III	28	10	2	2
Serum β_{2M}> 3.0 mg/l, no. of cases	4	1	0	0
Presence of osteolysis, no. of cases	51 (58%)	22 (50%)	3 (27%)	2 (29%)
Bone marrow plasma cell rate (median)	20%	20%	14	14

Table 2. Treatment methods in multiple myeloma patients with different long-term survival
Tabela 2. Metody leczenia chorych na szpiczaka plazmocytowego z różnym, długim czasem przeżycia

Treatment method	Number of patients with survival (%)			
	>7 years	>10 years	>15 years	>20 years
Melphalan	18 (20)	10 (20)	2 (18)	2 (28.6)
Melphalan followed by polychemotherapy	30 (35)	13 (30)	5 (46)	2 (28.6)
Polychemotherapy VMBCP/VABCP VMCP/VBAP	16 (18)	6 (14)	1 (9)	1 (14.2)
Chemotherapy and irradiation ^{60}Co, Rtx	15 (17)	10 (22)	3 (27)	2 (28.6)
Chemotherapy and Thalidomide, Bortezomib	9 (10)	6 (14)		
In total	88 (100)	45 (100)	11 (100)	7 (100)

Abbreviations: V – vincristine; M – melphalan; B – BCNU; C – cyclophosphamide, P – prednisone; A – adriblastine

The conventional chemotherapy in particular patients with long-term survival time was administered for many years; the doses of chemotherapeutics and breaks from the treatment were adjusted to bone marrow sufficiency status (i.e. values of leukocyte and platelets counts).

In 34% of cases during long-lasting treatment only stabilisation of the neoplasm process was achieved with the values of serum monoclonal protein concentration maintained at 3.0 g/dl.

Table 3. Treatment methods and response to treatment in multiple myeloma patients with long-term survival
Tabela 3. Metody leczenia i odpowiedź na leczenie u chorych na szpiczaka plazmocytowego z długim czasem przeżycia

Treatment method	Number of patients (%)	Number of patients with		Treatment duration till achieving plateau (months, range)	Plateau duration (months, range)	Longest survival (months)
		"good response"	stabilization			
Melphalan	18 (20)	8	10	3–89	22–240	396
Melphalan followed by polychemotherapy	30 (35)	12	18	5–82	6–104	236
Polychemotherapy VMBCP/VABCP VMCP/VBAP	16 (18)	15	1	5–28	14–96	265
Chemotherapy and ^{60}Co, Rtx	15 (17)	8	7	2–8	7–58	264
Chemotherapy and Thalidomide, Bortezomib	9 (10)	8	1	2–5	6–60	>155
In total	88 (100)	51 (66%)	37 (34%)	Median 10		

Abbreviations: V – vincristine; M – melphalan; B – BCNU; C – cyclophosphamide, P – prednisone; A – adriblastine

Table 4. Treatment and survival of particular patients with initially solitary plasmacytoma
Tabela 4. Leczenie i przeżycie poszczególnych chorych z pierwotnie odosobnioną postacią szpiczaka plazmocytowego

Case	Sex	Age/ years	Localization of tumor "solitary plasmacytoma"	Initial treat-ment of soli-tary lesion	Time from primary lesion occurrence to tumor generalization and onset of systemic treatment (months)	Systemic treatment	Overall survival (months)
1.	F	41	C VII, Th IV Spinal cord compression by tumor, limb paralysis	surgical, Rtx	156	M, VBCP, Rtx	264
2.	F	43	L-II	surgical	60	VAD, VMCP, VBAP, Bort, Thal	>180
3.	F	45	Th VI	surgical, Rtx	12	M, VMBCP	>123
4.	F	37	Th V-Th VIII	surgical, Rtx	24	VMBCP	> 96
5.	M	50	costae V-VII	surgical, Rtx	24	VMCP, VBAP	180
6.	M	40	iliac bone	Rtx	48	MP, VMCP	> 276
7.	M	52	humerus	no treatment	111	VMBCP, VABCP, ^{60}Co	192
8.	M	41	C II - C IV (osteolysis)	no treatment	36	VAD, VMCP, VBAP, Bort, Thal	143
9.	F	59	nasopharyngeal	surgical, ^{60}Co		VMBCP	132
10.	M	64	stomach	surgical	108	M	194
11.	F	30	toe	surgical	180 heel plasmacytoma	surgical ^{60}Co	>198
12.	M	50	nasopharyngeal	^{60}Co	no tumor symptoms	0	>300

Abbreviations: vertebrae C – cervical, Th-thoracic, L – lumbar; M – melphalan; V – vincristine; B – BCNU; A – adriblastin doxorubicine, D – dexamethasone; C – cyclophosphamide; P – prednisone; Rtx, ^{60}Co-irradiation; Bort – bortezomib; Thal – thalidomide

Table 5. Immediate causes of death of 61 multiple myeloma patients with long-term survival
Tabela 5. Bezpośrednie przyczyny zgonu 61 chorych na szpiczaka plazmocytowego z długim czasem przeżycia.

Cause of death	No of patients
1. Progression of plasma cell proliferation	35
2. Renal failure	3
3. Infection	5
4. Hepatic cirrhosis and digestive tract haemorrhage	1
5. Cardiac failure	2
6. Heart infarct	1
7. Thrombosis	1
8. Cerebrovascular incident	1
9. Car accident	1
10. Secondary neoplasms:	
– acute myeloid leukaemia	6
– bronchogenic cancer	2
– colon cancer	2
– nasopharyngeal cancer	1
Total	61

In 5 patients, initially treated with conventional chemotherapy, in whom stabilization of proliferative process was achieved, the administration of bortezomib and thalidomide in a phase of disease progression resulted in achieving response to treatment in form of a near complete remission lasting many months.

The patient with the longest, 33-year survival, was a 40-year- old woman, physician, who had been diagnosed with MM in 1975. At diagnosis, she presented with infiltration of bone marrow by plasma cells at the rate of 24% of all nucleated cells, presence of IgAκ monoclonal protein in serum at a concentration of 2.8 g/dl and absence of osteolytic lesions (disease stage I acc. D.S and ISS classification). Patient's myeloma diagnosis was confirmed in a reputable medical center in Paris, led by Professor Seligman,. Three melphalan courses were administered and then the patient was left without any anti-tumor treatment till the year 2004. She actively performed her job. M-protein concentration stayed at the range of 2.0–3.0 g/dl. Since the year 2000, M-protein concentration exceeded 3.0 g/dl. The patient progressed in December 2004; at that time the rate of bone marrow plasma cells was 57%, serum IgAκ M protein concentration amounted to 3.6 g/dl and osteolysis appeared. In the years 2005–2008, the patient was given melphalan and prednison therapy; she did not consent to any other therapy options. The patient deceased in September 2008 presenting symptoms of myeloma progression.

In 9 patients the diagnosis of multiple myeloma was preceded by detection of monoclonal protein in the serum. Time from M-protein finding to overt myeloma ranged from 6 months to 7 years. In 2 patients a monoclonal protein was revealed in the urine and time of evolution into myeloma was 12 and 18 months.

In a still alive patient with 25-year survival from the onset of anti-tumor treatment, myeloma diagnosis was preceded by a 6-year period of monoclonal gammopathy. In this woman, IgGκ monoclonal gammopathy had been revealed at the age of 46 years in 1978, while multiple myeloma was diagnosed in 1985. At myeloma diagnosis plasma cells constituted 36% of all nucleated bone marrow cells, IgGκ M-protein was present in the serum at the concentration of 2.49 g/dl, while no osteolysis was found. The patient was treated almost regularly with melphalan for the first 10 years; then she received melphalan courses only occasionally. Additionally, due to pathologic vertebral fractures, her spinal column was also irradiated. At present, the patient remains without anti-myeloma treatment. Her serum M-

protein concentration remains stable within values of 2.0–3.0 g/dl, and bone marrow plasma cell rate does not exceed 10–15%.

Treatment and survival of 12 patients with initially solitary plasmacytoma are presented in Table 4. In cases No 11 and No 12 no generalisation of plasma cell proliferative process was found till the last patient's observation. In case No 11, the primary site of plasmacytoma was the toe. The tumor was diagnosed in 1983 and the toe changed by neoplasmic process was amputated. Fifteen years later, in 1998, plasmacytoma of the heel of the same leg was found. Tumor was removed surgically and the site after tumor excision was irradiated with ^{60}Co. The patient remains without systemic treatment. In case No 12 of nasopharyngeal plasmacytoma, the patient after local irradiation with ^{60}Co remains free of disease symptoms for 25 years. The cases No 11 and 12 were not included into the analyzed group of 88 multiple myeloma patients with generalized disease and long-term survival.

Of 88 patients with survival time from the onset of anti-myeloma treatment exceeding 7 years, 12 remain still alive and are treated in Institute of Hematology and Blood Transfusion in Warsaw, 7 patients remain without treatment and the fate of one patient is unknown.

The causes of death of multiple myeloma patients with survival time over 7 years from the beginning of anti-tumor treatment are presented in Table 5. The cause of death in 6 patients was acute myeloid leukemia and in 5-solid tumors. In two patients with myeloid leukemia no plasma cell infiltrates were found at autopsy; it confirms eradication plasmocytic myeloma.

DISCUSSION

As shown in this study, the subset of long-term multiple myeloma survivors may be characterized at diagnosis as patient of age<55 years, with small tumor burden, normal serum calcium, creatinine and β2M concentrations, IgG monoclonal protein isotype and no cytogenetic abnormalities. In our study 50% of patients showed bone destruction and/or lytic changes (Table 1). Therefore, progressive bone lesions at disease onset probably are not a bad prognostic factor in myeloma patients with excellent outcome, as it was previously reported [21–26]. Even in an autopsy-documented myeloma cure 14 years after M-2 (melphalan, BCNU, cyclophoshamide, prednisone and vincristine) chemotherapy, that has been reported by van Hoeven [23], destructive bone lesions persisted radiographically but did not progress. The first-line chemotherapy (melphalan or its combinations with other chemotherapeutics) and the level of response were not prognostic factors for long-term survival. In one-third of patients only stable disease was observed (Table 3)

Complete remission was achieved in single cases; in two previously reported cases, in whom acute myeloid leukemia developed in the terminal disease phase, no evidence of myeloma was found at autopsy, which confirms cured myeloma [27, 28]. However, it is worth noticing, that in one case, despite no remission, stabilization of disease was observed without treatment for 23 years. Kyle [3] reported that prolonged disease- free survival was observed in 1/870 cases (0.11%) treated with conventional chemotherapy. Buckman et al. [2] reported the persistence of stable condition without treatment for over 7 years in 2/258 cases (0.78%). A few previously reported myeloma cases with prolonged disease free survival and treated with conventional chemotherapy were in complete remission for more than ten years and their disease condition represented "a cure" or "a state extremely close to cure"[22–26, 29, 30].

It is also worthy to notice that in our 5 patients, initially treated with conventional chemotherapy, in whom stabilization of disease was achieved, the administration of bortezomib and thalidomide in phase of disease progression resulted in near complete response [18, 31, 32].

In our studies, a real frequency of prolonged survivals of myeloma patients treated with conventional chemotherapy, in whom tumor was diagnosed before the year 2000, amounts to 14.7% while the proportion of survivals exceeding 10 years is 7.5%.

The introduction of high-dose chemotherapy for newly diagnosed myeloma has resulted in prolonged survival for the total patient population aged less than 60 years [33]. However, some trials have failed to demonstrate an overall survival advantage for this treatment modality compared to conventional chemotherapy [34, 35].

Arkansas group analyzed outcome using a logistic regression model in 515 consecutive multiple myeloma patients intended to receive melphalan-based tandem transplants with follow-up of> 5 years. One -quarter of patients had event- free survivals >5 years with no further relapses seen after 7 years (46 patients on plateau) [36]. The French group (IFM-94 trial; n=400) reported a 7 year overall survival of 42% patients with tandem-autologous stem cell transplantation versus 21% for a single transplant, with a median follow-up of 5 years [37]. In a British study of 167 myeloma patients who were planned to receive infusional chemotherapy plus an autograft, with minimum follow-up of 10 years, a 10-year survival was found in 23% of patients [38]. Moreau et al. [39] reported similar results. Among 127 patients treated with high-dose therapy, 4 were alive 79, 90, 132 and 153 months after transplantation. For a 10-year survival, the most significant variables predicting better outcome were β2M< 3.0 mg/L and patient's age<55 years.

Within the past decade new therapeutic options have been introduced for multiple myeloma, including autologous stem cell transplantation, thalidomide, lenalidomide, bortezomib and survival expectations of younger patients with this disease have increased [40–43]. Kumar et al. [40] analyzed the outcome of two groups of patients seen at a single institution, Mayo Clinic USA, to examine survival trends over time. One group was observed from the time of diagnosis while the other one – from the time of relapse. Among 387 patients relapsing after stem cell transplantation, an evident improvement in overall survival from the time of relapse was seen, with those relapsing after the year 2000 having a median overall survival of 23.9 versus 11.8 months (P<0.001) for those who relapsed prior to this date. This improvement was independent of other prognostic factors. The patients treated with one or more of the newer drugs (thalidomide, lenalidomide, bortzomib) showed longer survival from relapse (30.9 vs 14.8 months; P<.001). In a larger group of 2981 patients with newly diagnosed multiple myeloma, those diagnosed in the last decade had improvement in overall survival (44.8 vs 29.9 months; P<.001). In a Swedish population – based study [41], one-year, 5-year and 10-year survivals were compared over the years 1973 to 2003, and continuous improvement was seen during that time period, and as it was found in Kumar et al. study [40] the maximum improvement was seen in the last period of study covering the years 1994–2003. The maximum benefit was seen in the younger patients, especially those under 60 years of age at diagnosis.

Population-based studies done by Jawed et al. [42] using the Surveillance, Epidemiology and End Results Program (SEER) data base of the United States National Cancer Institute have also demonstrated improvement in the survival of myeloma patients in the past decade. In a study of 40538 patients with myeloma from SEER the years 1973–2003 the median survival was 24 months. Survival was better for females and for younger patients. Early treatment decade (1973–1985) was associated with diminished overall and cause-specific survival compared with the most recent studied time period covering the years 1996–2003.

Brenner et al. [43] estimated trends in age-specific 5-year and 10-year relative survival of patients with multiple myeloma in the United States from the years 1990–1992 to 2002–2004 from the 1973–2004 data base of the SEER Program [44]. Techniques of the period analysis were used to show most recent developments. Overall, 5-year relative survival increased from 28.8% to 34.7% (P<.001), and 10-year relative survival increased from 11.1% to 17.4% (P<.001) between 1990–1992 and 2002–2004. Much stronger increases were seen in the age group younger than 50 years, only moderate improvement was seen in the age group 60 to 69 years, and essentially no improvement was achieved among older patients [43].

According to standard practice in population-based cancer survival analysis, relative rather than absolute survival was calculated. Relative survival reflects survival of patients with cancer compared with

survival of the general population. It is calculated as the ratio of absolute survival of patients with cancer divided by the expected survival of a group of persons of corresponding sex, age and race in the general population [43].

Using data from the 1973–2005 data base of the SEER Program [45] Brenner et al.[46] employed a novel model – based projection method to project 5-year and 10-year relative survival expectations of multiple myeloma patients in the United States diagnosed in the years 2006–2010. Patients diagnosed with multiple myeloma in 2006–2010, especially those diagnosed at younger ages, are expected to have much higher long-term survival perspectives than suggested by previously available survival statistics.

Interpretation of population-based study outcomes by using various techniques of survival time statistical analysis and comparison of these results with the results of clinical studies must be very careful, since the spectrum of analyzed subjects is different. It should be also taken into account that the mean age of patients at multiple myeloma diagnosis amounts to approximately 65 years.

CONCLUSIONS

A real frequency of long-term survival of patients with multiple myeloma diagnosed till the year 2000 and treated with conventional chemotherapy amounts: 14.7% – for survival more than 7 years, 7.5% – for those longer than 10 years, 1.8% – of survival more than 15 years and 1.1% for those exceeding 20 years. In one-third of patients prolonged survivals occurred despite achieving only disease stabilisation on conventional treatment. Requirement of long-term survival was continuation of antitumor treatment for several years.

Population based studies with application of period analysis and a novel model – based projection method, new techniques of survival analysis, suggest that new therapeutic options have led in the recent years to increases in survival expectations of younger patients with multiple myeloma.

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