RESEARCH ARTICLE
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Survival Outcomes of Patients with Primary Plasma Cell Leukemia in the Era of Proteasome Inhibitors and Immunomodulatory Agents: A Real-Life Multicenter Analysis

Proteazom İnhibitörleri ve İmmünomodülatör Ajanlar Çağında Primer Plazma Hücreli Lösemili Hastaların Hayatta Kalma Sonuçları: Gerçek Yaşam Verilerinden Çok Merkezli Bir Analiz

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Abstract
Objective: In this study, we aimed to obtain real-life data on the use of antimyeloma agents, which significantly increase overall survival (OS) in multiple myeloma (MM) patients, in primary plasma cell leukemia (pPCL) patients with a poor prognosis.
Materials and Methods: Data from 53 patients who were diagnosed with pPCL between 2011–2020 and who used at least one proteasome inhibitor (PI) and/or immunomodulatory (IMID) agent were analyzed retrospectively. Depending on the year of pPCL diagnosis, 20% leukocytes or $\geq 2\times10^9$/L plasma cells in the peripheral blood were used.
Results: The median age of the patients was 58 years, and 23 (43.4%) patients were over 65 years of age. For first-line treatment, PI or IMID alone was used in 31 (58.5%) patients, and PI and IMID were used simultaneously in 15 (28.3%) patients. Additionally, 21 (39.6%) patients received transplantation, and 13 (24.5%) patients received maintenance treatment. The median progression-free survival was 4 (1–42) months. When patients whose primary disease was refractory to first-line therapy were excluded, the duration of treatment was 6.5 months. The median OS was 15 months, with a median follow-up of 15 months. Only 7 (13.2%) of the patients were alive at the last follow-up visit. Those with higher beta-2 microglobulin levels and ISS stage 3 and nontransplant patients receiving first-line treatment had shorter OS (p=0.005, p=0.02 and p=0.008, respectively). Otherwise, the concomitant use of PIs and IMIDs, the addition of chemotherapy to induction therapy, and the response to induction therapy or maintenance therapy did not affect OS.
Conclusion: In our study, as in previous similar studies, we could not see the increased survival trend in pPCL which is observed in MM. New studies are needed for pPCL patients, which is likely to increase with the new diagnostic criteria, based on current agents and information in MM.
Keywords: Primary plasma cell leukemia, Antimyeloma agents, Proteasome inhibitors, Immunomodulatory agents, Hematopoietic stem cell transplantation.

Öz
Amaç: Bu çalışma ile multipl miyelom (MM) hastalarında genel sağkalımda (OS) anlamlı bir artış sağlayan antimiyeloma ajanlarının, prognozu daha kötü olan primer plazma hücreli lösemi (pPHL) hastalarında kullanımına ilişkin gerçek hayat verilerini ortaya koymak istedik.
Gereç ve Yöntemler: 2011–2020 yılları arasında pPHL tanısı alan ve en az bir proteazom inhibitörü (PI) ve/veya immünomodülatör (IMID) ajan kullanan 53 hastanın verileri retrospektif olarak analiz edildi. Hastaların tanı yıllarından kaynaklı olarak, periferik kanda plazma hücresinin lökositlerin %20'sinden fazla veya $\geq 2\times10^9$/L olması pPHL tanı kriteri kabul edildi.
Bulgular: Hastaların ortanca yaşı 58 olup, 23 (%43,4) hasta 65 yaş üzerindeydi. İlk sıra tedavide 31 (%58,5) hastada PI veya IMID tek başına kullanılırken, 15 (%28,3) hastada PI ve IMID eş zamanlı kullanıldı. Ayrıca 21 (%39,6) hastaya nakil, 13 (%24,5) hastaya ise idame tedavisi uygulandı. Hastaların ortanca progresyonsuz sağkalım süresi 4 (1–42) aydı. İlk sıra tedaviye primer refrakter hastalar dışlandığında ise 6,5 aydı. Ortanca takip süresi 15 ay olan hastaların, ortanca OS süresi de 15 aydı. Son kontrolde hastaların sadece 7'si (%13,2) hayattaydı. Beta-2 mikroglobulin düzeyi yüksek, ISS skoru 3 olan ve birinci basamak tedavide nakil yapılmayan hastalarda OS daha kısaydı (sırasıyla, p=0.005, p=0.02 and p=0.008). Öte yandan indüksiyon tedavisinde PI ve IMID ajanlarının birlikte kullanılmasının, kemoterapi eklenmesinin, indüksiyon tedavisine yanıtın ve idame tedavisinin OS üzerine etkisi olmadığı görüldü.
Sonuç: Önceki benzer çalışmalarda olduğu gibi, çalışmamızda pPHL'de MM'de gözlenen artan sağkalım eğilimini göremedik. Yeni tanı kriteri ile birlikte artması olası pPHL hastaları için, MM'daki güncel ajanlar ve bilgiler dahilinde, yapılacak yeni çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Primer plazma hücreli lösemi, Antimiyelom ajanlar, Proteazom inhibitörleri, İmmünomodülatör ajanlar, Hematopoietik kök hücre nakli.

Introduction

The diagnostic criterion for plasma cell leukemia (PCL), which was first defined in 1974 as the detection of more than 20% leukocytes or $\geq 2\times10^9$/L plasma cells with monoclonal gammopathy in peripheral blood, was revised in 2018 to the detection of more than 5% leukocytes or $\geq 0.5\times10^9$/L plasma cells in peripheral blood [1,2,3]. Since the prognosis of high-risk MM patients with circulating plasma cells in the peripheral blood is as poor as that of pPCL patients, >2% has been suggested as the optimal prognostic threshold for flow cytometry [4,5]. PCL, which accounts for approximately 1–2% of all plasma cell dyscrasias, occurs in two forms, primary (de novo) and secondary, which develops in patients who have previously been diagnosed with multiple myeloma. Patients with primary PCL (pPCL), which accounts for approximately 60% of PCL cases, are younger than patients with secondary PCL (sPCL) [2,6]. Both types have a worse prognosis than multiple myeloma (MM), but sPCL has a worse prognosis than pPCL does [7,8].

Over the last 20 years, the use of proteasome inhibitors (PIs), immunomodulatory agents (IMIDs), and targeted drugs in various combinations, as well as autologous hematopoietic stem cell transplantation (HSCT) and maintenance therapy, in conjunction with a clearer treatment algorithm, has resulted in a significant improvement in overall survival (OS) of MM patients [9]. Although agents and treatments that are effective for MM have been used in pPCL patients in recent years, no substantial improvement in terms of OS has been reported compared with MM patients. The 4-year OS rate of pPCL patients is still approximately 30%, despite the use of HSCT [10,11]. According to an analysis based on the Surveillance, Epidemiology, and End Results (SEER) database by Gonsalves et al., the median survival times of patients with pPCL were 5, 6, and 4 months from 1973-1995, 1996-2000, and 2001-2005, respectively. The median OS of patients diagnosed between 2006 and 2009, which coincided with the use of the first antimyeloma agent, was 12 months [12]. The use of bortezomib, thalidomide, lenalidomide, and HSCT has been reported to improve OS and progression-free survival (PFS) [13-19]. However, with the increasing use of antimyeloma agents in the following period, it is not clear whether a trend similar to that of MM occurred in PCL, whose treatment algorithm is not yet clear.

Therefore, with this multicenter retrospective study, we aimed to reveal the current real-life data of pPCL patients in whom new PIs, IMIDs, and monoclonal antibodies, which are increasingly being used in MM, were also used.

Materials and Methods

The archival records and clinical and laboratory data of patients diagnosed with PCL at 19 centers in Turkey between January 2011 and December 2020 were retrospectively analyzed. Patients with pPCL who met the 2003 International Myeloma Working Group (IMWG) diagnostic criteria for PCL (detection of more than 20% leukocytes or $\geq 2\times10^9$/L plasma cells in peripheral blood) instead of the new diagnostic criteria due to the years of diagnosis of the patients included in the study [2-5], who were over 18 years of age, and who received at least one series of PI and/or IMID treatments were included in the study (5 patients who received the VAD (vincristine, adriamycin and dexamethasone) protocol, which did not include PI and/or IMID agents in induction, were included in the study because these agents were used in subsequent treatment processes). Patients with sPCL were excluded.

For each patient, baseline data were collected at the time of diagnosis, and information on all-line therapies and patient responses was collected. Responses to treatments were evaluated according to the IMWG response criteria [20]. The primary outcome evaluated was OS, which was measured from the date of diagnosis to the time of last follow-up or death. The impacts of HSCT and maintenance therapy **on OS, as well as PFS,** were the secondary outcomes of interest. Death within the first 3 months due to disease or treatment side effects was defined as early death.

Statistical Analysis

IBM SPSS Statistics (version 24) was used for the statistical analysis. Descriptive statistics were used to present the data. Categorical data are presented as numbers and ratios, and numerical data are presented as medians, minima, and maxima. Significant differences between the data were analyzed using the Mann–Whitney U test for independent variables. OS was defined as the duration from the date of the first day of treatment to the date of death or time to the survivors' last follow-up. Kaplan–Meier survival analysis was applied for OS, and log-rank tests were used to examine the factors affecting survival. Cox regression analysis was applied to evaluate factors affecting survival. Differences with p values ≤ 0.05 were considered statistically significant.

Results

Patients

A total of 54 patient records were obtained from 19 different centers in Turkey. One patient was excluded from the study because of exitus without any treatment, and the data of 53 patients who used at least one series of PIs and/or IMIDs were analyzed. The demographic and clinical characteristics of the patients are presented in Table 1.

All patients received at least one line of treatment, with a maximum of 4 lines. During first-line therapy, 21 (39.6%) patients underwent HSCT, and 13 (24.5%) patients received maintenance therapy. Thirty-two (60.4%) patients underwent second-line treatment, and 19 (35.8%) patients underwent SCT after second-line treatment. Sixteen (30.2%) patients received third-line treatment, and 5 (9.4%) patients received fourth-line treatment. During the entire treatment period, 51 (96.2%) of 53 patients received bortezomib, 34 (64.2%) received lenalidomide, 16 (30.2%) received thalidomide, 9 (16.9%) received carfilzomib, 5 (9.4%) received pomalidomide, 5 (9.4%) received daratumumab, 2 (3.7%) received ixazomib, 2 (3.7%) received venetoclax, and 26 (49%) received chemotherapy (PACE combined with antimyeloma agents in 25 and DCEP in 1).

First-line Treatment

First-line treatment comprised 9 different treatment protocols. Except for five patients who were given VAD treatment, bortezomib was used as the PI, and/or thalidomide and lenalidomide were used as the IMID. The distribution of patients and response to these treatments according to the regimens used in induction treatment and the distribution of agents used in maintenance treatment are given in Table 2. The mean duration from diagnosis to transplantation was 5.5 (range: 3-10) months. Nine out of the 13 patients who received maintenance

treatment had to be discontinued because of side effects (1 patient) and disease progression (8 patients). Three patients were still alive and continued to receive maintenance treatment (one other patient was lost to follow-up). The median duration of maintenance therapy was 6.5 (range: 1–20) months. The median time to progression after first-line treatment was 4 (range: 1–42) months.

Treatment of Relapsed/Refractory Patients

Thirty-two patients (60.3%) received second-line treatment with 9 different treatment protocols. After second-line treatment, the median time to progression after transplantation was 6 (range: 1–31) months. The 16 (30.2%) patients who were alive with or without transplantation after second-line treatment and who received third-line treatment due to progression received 11 different protocols. The median duration of third-line treatment was 4 (range: 1–24) months. Four different treatment protocols were applied to 5 (9.4%) patients who received fourth-line treatment. With respect to fourth-line treatment, one patient who achieved a partial response to pomalidomide and dexamethasone treatment survived for 55 months, whereas progression and death occurred within 2 months in the other 4 patients. Table 3 shows the treatment distribution and response status of the patients with relapsed/refractory disease.

Survival

The median PFS was 4 (1–42) months. When early deaths were excluded, the median PFS was 5 months, and when patients whose primary disease was refractory to first-line therapy were excluded, it was 6.5 months. PFS was similar in patients aged ≥65 years (p=0.11), those with International Staging System (ISS) stage 3 and 1-2 disease (p=0.54), those who received and did not receive PI and IMID combinations as first-line therapy (p=0.45), and those who received and did not receive intensive chemotherapy with antimyeloma agents as first-line therapy (p=1.0). However, the median PFS of patients who were able to receive transplantation as first-line therapy was longer than that of patients who were not able to receive transplantation (p<0.001) (Figure 1).

The median OS was 15 months (95% CI: 10–19), with a median follow-up of 15 (range: 1–131) months. The OS rate was 13.2% after a median follow-up of 15 months. Only 7 (13.2%) of the patients were alive at the last follow-up visit because 46 (86.3%) patients (30 due to disease and 16 due to nondisease causes) died. In the first three months, nine patients died, for an early mortality rate of 17%. The median OS of patients other than these patients was 19.5 (range: 1–131) months.

According to the univariate analysis, the OS of patients older than 65 years was 12 months (95% CI: 2–21), and the OS of patients younger than 65 years was 19 months (95% CI: 14–23); however, the difference was not statistically significant (p=0.076). There was no statistically significant difference in OS between the sexes (p=0.054). Those with high beta-2 microglobulin levels had shorter OS (p=0.005) than those with low beta-2 microglobulin levels. **In addition, patients with ISS 3 stage disease had shorter OS than patients with ISS 1–2 stage disease did (p=0.02) (Figure 2).** In terms of induction therapy, 15 patients (28.3%) who received IMID and PI drugs simultaneously and those who did not (p=0.76) had similar OS (Figure 3A), as did 9 patients (16.9%) who received intense chemotherapy with antimyeloma agents and those who did not (p=0.79) (Figure 3B). Although the OS of 28 (52.8%) patients who achieved at least partial response (PR) (complete response, very good partial response, and PR) after induction therapy was 18 months (95% CI: 16–36) and that of 14 patients who achieved <PR (minimal response, stable disease and progression) was 10 months (95% CI: 7–53), the difference was not statistically significant (p=0.64) (Figure 3C). Although nontransplant patients had a shorter OS than transplant recipients did in first-line treatment (p=0.008, HR=2.3) (Figure 3D), maintenance therapy was not correlated with OS (p=0.24). Only beta-2 microglobulin was found to be correlated with OS (p=0.04, HR=1.05) in a multivariate analysis that included beta-2 microglobulin and transplantation during first-line treatment.

Discussion

A mean OS of 15 months was revealed by our retrospective analysis of 53 pPCL patients who were diagnosed between 2011 and 2020 at 19 different sites. We identified different potential therapeutic regimens comprising various drug combinations of both induction therapy and second-line treatment. Additionally, new drugs that are more potent and have different mechanisms, which contribute positively to OS in patients with MM, were administered to a small number of patients.

In various nations and continents, few studies in the literature have attempted to determine the OS of pPCL patients during the period when antimyeloma drugs were more widely employed. As far as we determined, the number of patients included in the studies conducted in the period when new agents were used in the foreground was lower than the number of patients included in our study, except for two studies. In these studies involving more than 10 (11-117) pPCL patients, the mean OS was reported to be between 14 and 33 months [21-28]. In the study of Mina et al., who reported the longest OS of 33 months, the combined use of PI and IMID during induction (92%), HSCT (74%), and maintenance therapy (60%) rates were higher than those reported in other studies [28]. Ganzel et al., who reported that the OS time of 39 patients was the same as that in our study, reported early death in 18% of patients and that the OS of patients who did not die in the first 3 months was 22.5

months. In addition to age and/or morbidity, early death is another reason for consolidative transplantation not being performed, likely affecting OS.

Previous studies have shown that pPCL patients who use new agents, particularly bortezomib and lenalidomide, which are antimyeloma agents that are increasingly used and are the most discussed antimyeloma agents in this field, experience longer OS than those who do not [13,18,19,22,23,27,29-31]. Although all patients in our analysis used PI (96.2% bortezomib) and/or IMID (64.2% lenalidomide) at least once, the percentage of patients who used PI and IMID together (triplet) for induction therapy (28.3%) was low. This may be the reason why we were unable to demonstrate its advantage in terms of OS. In a recent phase 2 study (EMN12/HOVON129), PFS and OS were found to be longer in both young and older PCL patients after induction, consolidation and maintenance treatment with carfilzomib, a more potent PI, and lenalidomide than in previous studies. However, as with other studies, the results were not satisfactory with respect to improvements in MM. In addition, despite the greater responses obtained after induction with KRd, no significant relationship could be shown between the depth of response and OS, as in our study [32].

Mina et al. reported that adding intensive chemotherapy to new agents during induction treatment did not improve PFS or OS, as in our study [28]. On the other hand, Pena et al. reported that adding intensive chemotherapy provided an OS advantage [22]. Information on whether the use of intensive chemotherapy, which was also used in the years when antimyeloma agents were not used and the OS was less than 12 months, in combination with antimyeloma agents, which are more potent today, will improve OS is contradictory, and more studies are needed in this direction. However, the addition of intensive chemotherapy to new agents is still recommended, especially for young patients [33].

Many studies have revealed that patients who undergo consolidative upfront HSCT experience longer OS than those who do not [21,27,34]. However, a small number of studies failed to demonstrate a similar advantage. Although Pena et al. demonstrated the advantage of HSCT in univariate analysis, this advantage was lost in multivariate analysis, as in our study [22]. Additionally, Mina et al. demonstrated the PFS advantage of upfront autologous HSCT but failed to demonstrate the OS advantage [28]. According to the records of the European Society for Blood and Marrow Transplantation (EBMT), there was an increase in transplantation rates for pPCL patients from 1998 to 2014, and the median OS of all patients was 33 months, regardless of the type of transplantation. In addition, complete remission before transplantation has been shown to provide a major OS benefit [35]. Providing a deep response with more potent antimyeloma agents, such as the KRd used in the EMN12/HOVON 129 study, and determining the appropriate transplantation strategy, are considered the most appropriate approaches [32,35].

In Mina et al.'s study, although maintenance therapy improved PFS, it did not significantly improve OS. In contrast to our study, in which a single agent was largely utilized in maintenance therapy (77% of patients) and no OS advantage could be demonstrated, in this study, we thought that dual agent (PI and IMID) use in maintenance therapy, as in the EMN12/HOVON 129 study, was advantageous in the majority of patients (87%) [28,32].

Almost all studies similar to our study were conducted in pPCL patients who met the diagnostic criteria determined in 2003 [2]. Among the studies that compared the OS durations of patients with peripheral blood plasma cells ≥20% with those between 5% and 19% and found them to be similar, the Spanish study reported OS of 6 months and 14 months, respectively; the MAYO Clinic study reported 13 months in both groups [3,36]. Subsequently, in 2021, the IMWG lowered the threshold from 20% to 5% to better reflect the high-risk nature of PCL patients [37]. After the new definition, it has aroused curiosity as to whether there are similar results. In this regard, some studies have re-evaluated patients diagnosed in the past, and the survival times of patients with ≥20% plasma cells in peripheral blood and those with 5–19% plasma cells were found to be similar [30,31,34]. However, the latest recommendation in this direction is that it should be above 2% [4,5].

In addition to being a retrospective study, the most important limitation of our study was that we could not access demographic data and also failed to obtain cytogenetic features such as t(11;14), which is common in pPCL; therefore, we could not perform risk classification **(Revised MM ISS)** or evaluate the patients in these respects because patients from different years and centers were included. Additionally, patients diagnosed with pPCL with the diagnostic criteria of 2003 were included in the study, depending on the year of diagnosis. Therefore, since patients with lower peripheral blood plasma cell ratios were not included in our study and data on the number and ratio of plasma cells in peripheral blood were not available, analysis in this direction could not be performed. Finally, treatment protocols were quite different due to center experience and differences in access to agents due to the number of years of diagnosis, age, and performance. This prevented us from performing adequate analysis in terms of response status and survival according to treatments. Therefore, patients had to be grouped and analyzed according to their use of PIs and IMIDs.

Conclusion

In most retrospective studies, as in our study, there are nonstandardized treatment approaches applied for different reasons that were developed based on MM treatment. Although these studies have different results and direct comparisons cannot be made, new antimyeloma agents and HSCT seem to provide partially positive

results for the survival of pPCL patients. However, there is insufficient information on the necessity of using intensive chemotherapy in addition to new agents and which agent(s) should be used for maintenance therapy. The new definition is likely to increase the number of pPCL patients. Current studies and good registries, with the support of historical information in the literature and current MM approaches, may be helpful in identifying the optimal treatment approaches for pPCL.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Akdeniz University Faculty of Medicine and was conducted in accordance with the principles outlined in the Declaration of Helsinki and all applicable regulations (Ethics Committee date and approval number: 28/04/2021/KAEK-201).

Informed Consent: Informed written consent was not obtained because of the retrospective nature of the study.

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Authorship contributions: U.A., O.S. and U.I. conceived the study. All authors collected data on patients treated at their centers. U.A., T.U., O.S., O.K.Y., U.I. and L.U. analyzed the collected data and wrote the manuscript. All authors checked the results, read, critically reviewed and approved the manuscript.

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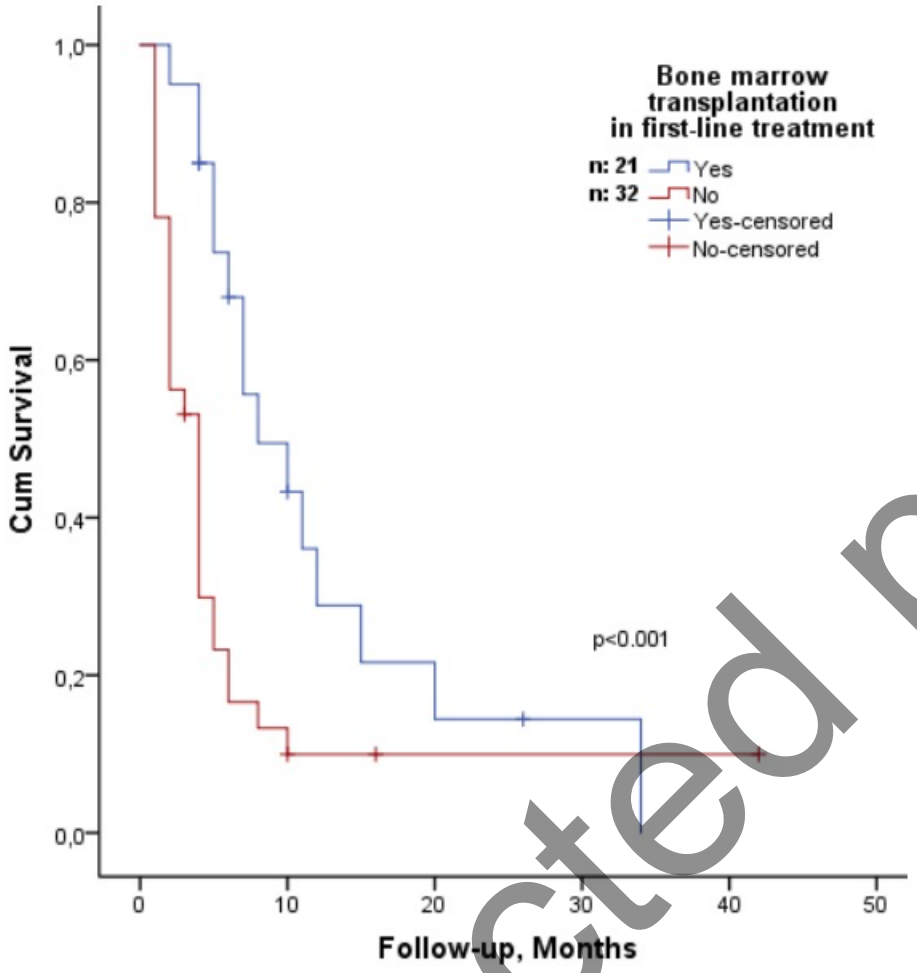

Figure 1: Progression-free survival in patients with and without bone marrow transplantation in first-line therapy; **n,** number of patients

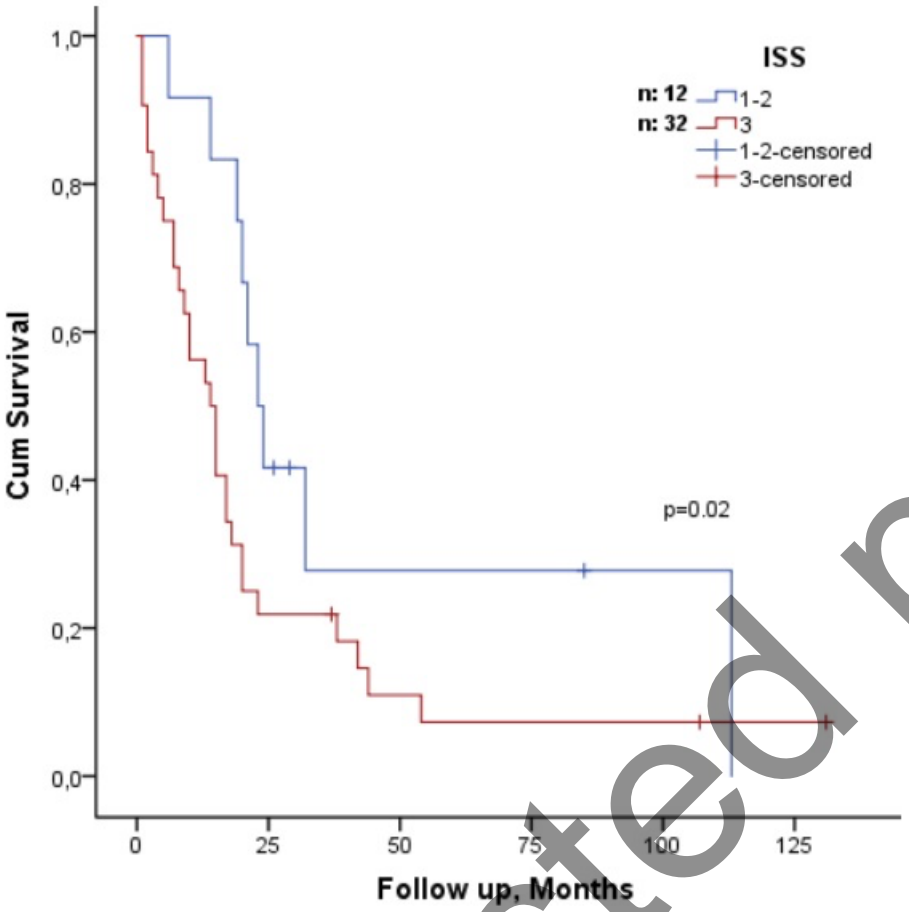

Figure 2: Comparison of overall survival of International Staging System (ISS) stage 1-2 and 3 patients; **n,** number of patients

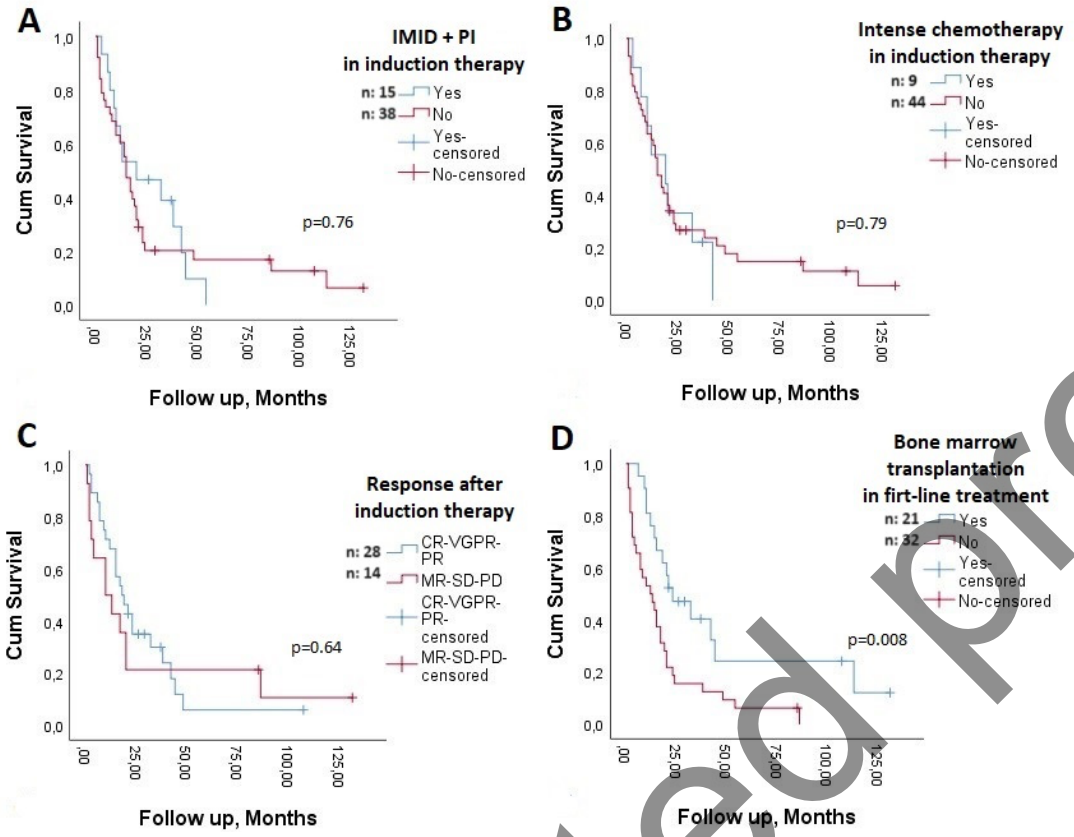

Figure 3: A) PI and IMID used together and not used in induction therapy; **B)** in induction treatment, with or without intensive chemotherapy with an antimyeloma agent; **C)** after induction therapy, patients with or without at least a PR; **D)** patients with or without consolidative bone marrow transplantation in first-line therapy; **n,** number of patients

Table 1. Demographic and clinical characteristics of the patients.

Characteristics		Number
Age (Median)		58 (24-84)
	>65	23 (43.4%)
	<65	30 (56.6%)
Sex	Female	20 (37.7%)
	Male	33 (62.3%)
Comorbidity	Hypertension	14 (26.4%)
	Chronic Kidney Disease	11 (20.8%)
	Coronary Artery Disease	7 (13.2%)
	Chronic Obstructive Pulmonary Disease	6 (11.3%)
	Diabetes Mellitus	4 (7.5%)
	Heart Failure	2 (3.8%)
	Chronic Liver Disease	2 (3.8%)
	Alzheimer	2 (3.8%)
	Solid Cancer	2 (3.8%)
M-Protein type	IgG_kappa	16 (30.1%)
	IgG_lambda	9 (16.9%)
	IgA_kappa	4 (7.5%)
	IgA_lambda	3 (5.7%)
	Light chain (kappa/lambda)	16 (9/7) (30.1%)
	Nonsecreting	3 (5.7%)
	Unspecified	2 (3.8%)
Laboratory	Hemoglobin, g/dL, median (range)	8.68 (4.6-12.8)
	Creatinine, mg/dL, median (range)	1.34 (0.4-11.6)
	Calcium, mg/dL, median (range)	9.96 (7.4-17.6)
	β2 microglobulin, mg/L, median (range)	8.4 (2.0-38.7)
ISS staging	ISS-1	5 (9.4%)
	ISS-2	7 (13.2%)
	ISS-3	32 (60.3%)
	Not available	9 (16.9%)
Ig: Immunoglobulin, ISS: International Staging System, WBC: White blood cells.		

Table 2. Distribution of induction regimens, consolidative transplants, maintenance therapy, and treatment responses.

		Number of Patients (%)
Induction treatment		**53**
	Only PI based	29 (54.7)
	Only IMID based	2 (3.7)
	PI and IMIDs based	8 (15.1)
	PI and/or IMIDs + PACE	9 (16.9)
	*Only VAD	5 (9.4)
Response to induction therapy	CR / VGPR	8 (15.1) / 13 (24.5)
	PR / MR	7 (13.2) / 5 (9.4)
	SD / Progression	6 (11.3) / 3 (5.7)
	Unspecified	11 (20.8)
HSCT	Yes (Autologous / Allogeneic)	**21** (20 / 1) (39.6)
	No	**32** (60.4)
Maintenance		**13** (24.5)
	Lenalidomide	7 (13.2)
	Bortezomib	3 (5.6)
	PIs and IMIDs combination	3 (5.6)
Final status after first-line treatment		**51**
	Refractory	22 (41.5)
	Relapse	20 (37.7)
	Remission	9 (16.9)

CR: Complete response, HSCT: Hematopoietic stem cell transplantation; IMIDs: Immunomodulatory agents, MR: Minimal response, PACE: Cisplatin, doxorubicin, cyclophosphamide, etoposide; PIs: Proteasome inhibitors, PR: Partial response, SD: Stable disease, VAD: Vincristine, adriamycin, dexamethasone, VGPR: Very good partial response.

Only PI based: VD: Bortezomib, dexamethasone, VCD: Bortezomib, cyclophosphamide, dexamethasone; Only IMID based: MPT: Melphalan, prednisone, thalidomide; PI and IMIDs based: VRD: Bortezomib, lenalidomide, dexamethasone, VTD: Bortezomib, thalidomide, dexamethasone; PI and/or IMIDs + PACE: VCD or VTD + PACE.

*PI (bortezomib) and/or IMIDs (lenalidomide and thalidomide) were used in the subsequent treatment processes of the patients.

Table 3. Distribution of second-, third- and fourth-line treatment regimens, transplants after second-line treatment and response to treatments.

		Number of Patients (%)
Second-line treatment		**32**
	Only PI based	5 (15.6)
	Only IMID based	7 (21.8)
	PIs and IMID based	12 (37.5)
	PI and IMIDs + PACE	6 (18.7)
	DRd	1 (3.1)
	Venetoclax	1 (3.1)
Response to second-line treatment	CR / VGPR	6 (18.7) / 8 (25)
	PR / MR	5 (15.6) / 1 (3.1)
	SD / Progression	1 (3.1) / 2 (6.2)
	Unspecified	9 (28.1)
HSCT after second-line treatment		**19 (59.3)**
	Autologous	5 (15.6)
	Allogeneic	11 (34.3)
	Autologous and allogeneic	3 (9.3)
Response after HSCT	CR / VGPR	5 (26.3) / 6 (31.6)
	PR / MR	0 (0) / 0 (0)
	SD / Progression	1 (5.3) / 3 (15.8)
	Unspecified	4 (21.1)
Third-line treatment		**16**
	Only PIs based	2 (12.5)
	Only IMIDs based	7 (43.7)
	PIs and IMIDs based	3 (18.8)
	DVd	2 (12.5)
	Venetoclax	1 (6.3)
	DCEP	1 (6.3)
Response to third-line treatment	CR / VGPR	1 (6.3) / 0 (0)
	PR / MR	0 (0) / 0 (0)
	SD / Progression	2 (12.5) / 8 (50)
	Unspecified	5 (31.2)
Fourth-line treatment		**5**
	Only PI based	1 (20)
	Only IMID based	2 (40)
	PI and IMID based	1 (20)
	DVd	1 (20)