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Authors

Gowda, Lohith
Shah, Mithun
Badar, Ifra
et al.

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Primary Plasma Cell Leukemia: Autologous Stem Cell Transplant in an Era of Novel Induction Drugs

Lohith Gowda[1], **Mithun Shah**[2], **Ifra Badar**[3], **Qaiser Bashir**[3], **Nina Shah**[4], **Krina Patel**[5], **Rashmi Kanagal-Shamanna**[6], **Rohtesh Mehta**[3], **Donna M. Weber**[5], **Hans C. Lee**[5], **Elisabet E. Manasanch**[5], **Abdul Shah**[3], **Sheeba K. Thomas**[5], **Simrit Parmar**[3], **Yago Nieto**[3], **Robert Z. Orlowski**[5], **Richard Champlin**[3], **Muzaffar H. Qazilbash**[3,*]

[1]Division of Hematology, Yale School of Medicine, New Haven, CT 06511

[2]Division of Hematologic Malignancies, Mayo Clinic, Rochester, MN 55905

[3]Department of Stem Cell Transplant, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030

[4]Division of Hematology, University of California San Francisco, CA 94143

[5]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030

[6]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030

Introduction

Plasma cell leukemia (PCL) is a rare and aggressive variant of multiple myeloma (MM) that could either develop de-novo (called primary PCL- pPCL) or as leukemic transformation of underlying MM (called secondary PCL- sPCL). Induction chemotherapy with an alkylator-based combination has shown modest responses in PCL with a median overall survival (OS) of less than a year[1]. In MM, proteasome inhibitors (PIs) and immunomodulatory drugs (IMIDs) followed by consolidation with an autologous hematopoietic stem cell transplantation (auto-HCT) has significantly improved outcomes. A similar benefit in treating pPCL with PIs and IMIDs in pre and post auto-HCT setting needs validation [2–4].

To assess progress in pPCL management, we performed a retrospective analysis of adult patients (≥18yrs, n=23) that received auto-HCT at MD Anderson Cancer Center between 2000–2016. pPCL was defined as the presence of absolute plasma cell count ≥ 2×10^9/l and/or ≥ 20% of peripheral white blood cell (WBC) count. Response to induction therapy was based on the International Myeloma Working Group (IMWG) criteria [5]. Patients were deemed to have high-risk disease if conventional cytogenetics in at least 2 metaphases showed t (4;14), t (14;16), t (14;20), −17/del(17p), −13/del(13q), hypodiploidy (<45 chromosomes excluding −Y), or chromosome 1q amplification or 1p deletion. Furthermore, they were also considered high-risk if fluorescence *in situ* hybridization (FISH) detected t

*Corresponding Author: Mqazilba@mdanderson.org.

(4;14), t (14;16), t (14;20) or del 17p13, amplification 1q or del 1p at the time of diagnosis. Primary outcomes evaluated were progression-free survival (PFS) and overall survival (OS). Best response post auto-HCT and the impact of maintenance therapy were the secondary outcomes of interest. Kaplan-Meier product limit estimates were used to calculate the probabilities of OS and PFS. Statistical analyses were performed using Statistica software with a significance level of 0.05.

Results

Demographics and disease characteristics are summarized in Table 1. The median dose of CD34+ cells infused was 4.0×10^6/kg (Range 2.5–12.9). There were no graft failures post-transplant with a median time to neutrophil and platelet engraftment of 11 days (range 10–14 days) and 13 days (range 8–23 days) respectively.

Induction, Conditioning and Maintenance Therapy:

All patients (n=23) received PI or IMiDs, either alone or in combination with steroids prior to auto-HCT. Four (17.3%) and 2 (11.7%) patients needed second and third-line therapies pre-transplant. Response to induction or latest salvage therapy was as follows: complete response (CR)/stringent CR (sCR) in 3 (13%), near CR (nCR) in 3 (13%), very good partial response (VGPR) in 4 (17%), partial response (PR) in 5 (22%), stable disease (SD) in 3 (13%) and progressive disease (PD) in 5 (22%) patients. Five (22%) received PI ± steroids, two (8%) IMiD ± steroids, seven (30%) triplets (PI ± IMiD ± Steroids) and 9 (39%) received PI or IMID in combination with chemotherapy as frontline induction therapy. Chemotherapy based regimens included VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide referred as) or mCBAD (cyclophosphamide, bortezomib, doxorubicin, dexamethasone) or bortezomib, thalidomide/lenalidomide, cyclophosphamide ± steroids. Transplant conditioning was done with melphalan 200 mg/m^2 in 19 (82%), combination of gemcitabine, busulfan and melphalan in 2 (8%), combination of melphalan, cyclophosphamide, and topotecan in 1 (4%), and melphalan with lenalidomide in 1 (4%) patient. Twelve (52%) patients received post auto-HCT maintenance therapy as a posttransplant consolidation strategy (Table 2). Median duration from the time of auto-HCT to the start of maintenance was 4.0 months (range 0.8–18.5). (Table 2).

Post Transplantation Outcomes

Best post auto-HCT response was CR in 6 (26%), nCR in 1 (4%), VGPR in 4 (17%) and PR in 6 (26%) with an overall response rate of 74%. After a median follow up of 18.1 months, the median progression-free survival (PFS) and overall survival (OS) was 5.5 and 18.1 months, respectively. Nineteen (95%) patients died of relapse, and 1 (5%) due to infectious complication. On univariate analyses, use of post-transplant maintenance was associated with a longer PFS (16.9 vs. 3.9 months, p=0.05) and a trend towards a longer OS (31.8 vs. 16.1 months, p=0.07) (Figure 1 and 2). Median PFS in patients with high-risk chromosomal abnormalities was 3.9 months vs. 19.2 months in patients without high-risk chromosomal abnormalities (p=0.01). However, there was no significant difference in OS between patients with or without high-risk chromosomal abnormalities (17.6 vs. 31.8 months, p=0.21).

Our results suggest that auto-HCT for pPCL, particularly in combination with post transplant maintenance therapy, is an effective treatment and may prolong disease remission and survival. Outcomes for patients receiving PIs or IMiDs pre-transplant are superior to historical controls that received alkylator-based chemotherapy.

pPCL is marked by early relapse and mortality, mainly due to resistance to existing therapy [2]. Historically, approximately 1 out of 4 pPCL patients died within a month of diagnosis, with a median OS of 7 months [3, 6]. A prior study, which evaluated the efficacy of induction chemotherapy using conventional cytotoxic agents (vincristine, melphalan, cyclophosphamide, prednisone (VMCP) and adriamycin, or vincristine, adriamycin, and dexamethasone (VAD), or intermediate doses of melphalan) reported a an overall response rate (ORR) of 29% [7]. However, the use of PIs and IMiDs in the last 15 years has been associated with an improved response rate of >70% [4, 6, 8–11]. Consistent with these recent studies, the ORR in our study was 74%, again highlighting the impact of PIs and IMiDs in the induction therapy for pPCL.

High proliferation rates and adverse disease biology are the main drivers of poor outcomes in pPCL. To prevent rapid relapses, initial gains made with induction therapy need subsequent transplantation and maintenance strategies[9]. Addressing the question of an appropriate post-induction strategy, a large registry study showed superior outcomes with upfront auto-HCT over allo-HCT (3-year OS; 64% vs 39%)[3]. Although relapse rates were lower with allo-HCT, high treatment related mortality (TRM) (41% vs 5%) offset the benefits of allo-HCT compared with auto-HCT. Based on these observations, auto-HCT seems to be the preferred approach. The median PFS and OS in our study were 5.5 and 18 months, respectively, from the time of auto-HCT, with post-transplant relapse (95%) being the dominant cause of death. This warrants approaches to reduce relapse rate, perhaps with aggressive post-auto-HCT strategies. These approaches include either tandem auto-HCT, or auto followed by a reduced intensity allo-grafting. To address this question, a recent French study in a landmark analysis from the time of second transplant showed a superior OS (median not reached) for tandem-auto (n=7) vs 28.6 months with auto + allo (n=17) approach[9]. Alternatively, use of post auto-HCT consolidation and maintenance is another feasible option[12]. Nooka et al have shown promising outcome with post-transplant combination therapy in high-risk myeloma [13]. Jakubowiak et al also demonstrated the potential benefit of post-transplant consolidation with a combination of carfilzomib, lenalidomide and dexamethasone[14]. Based on our retrospective experience, we showed better PFS (16.9 vs 3.9 months, p 0.05) and a trend towards improved OS (31.8 vs 16.1 months, p 0.07) in patients who received post-transplant maintenance. With the advent of newer PIs and monoclonal antibodies, we may see further improvement in PFS by using these newer approaches.

Our report is one of the larger single center experience for pPCL patients receiving auto-HCT with novel induction drugs. Despite encouraging findings, there are limitations to our study. We only included pPCL patients that received auto-HCT. Due to the nature of referral practice, we are unable to comment on patients who were not referred for transplant, hence our findings could not be generalized for non-transplant recipients. Use of maintenance

drugs showed significant improvement in PFS in this study and warrants future study to address this question in a prospective design.

In conclusion, our study shows that auto-HCT is safe, feasible and can potentially improve the outcome for pPCL patients if given with PI or IMiD-based induction and post-transplant maintenance therapy. However, more work needs to be done to better understand the biology of this aggressive disease and to develop more effective treatment approaches.

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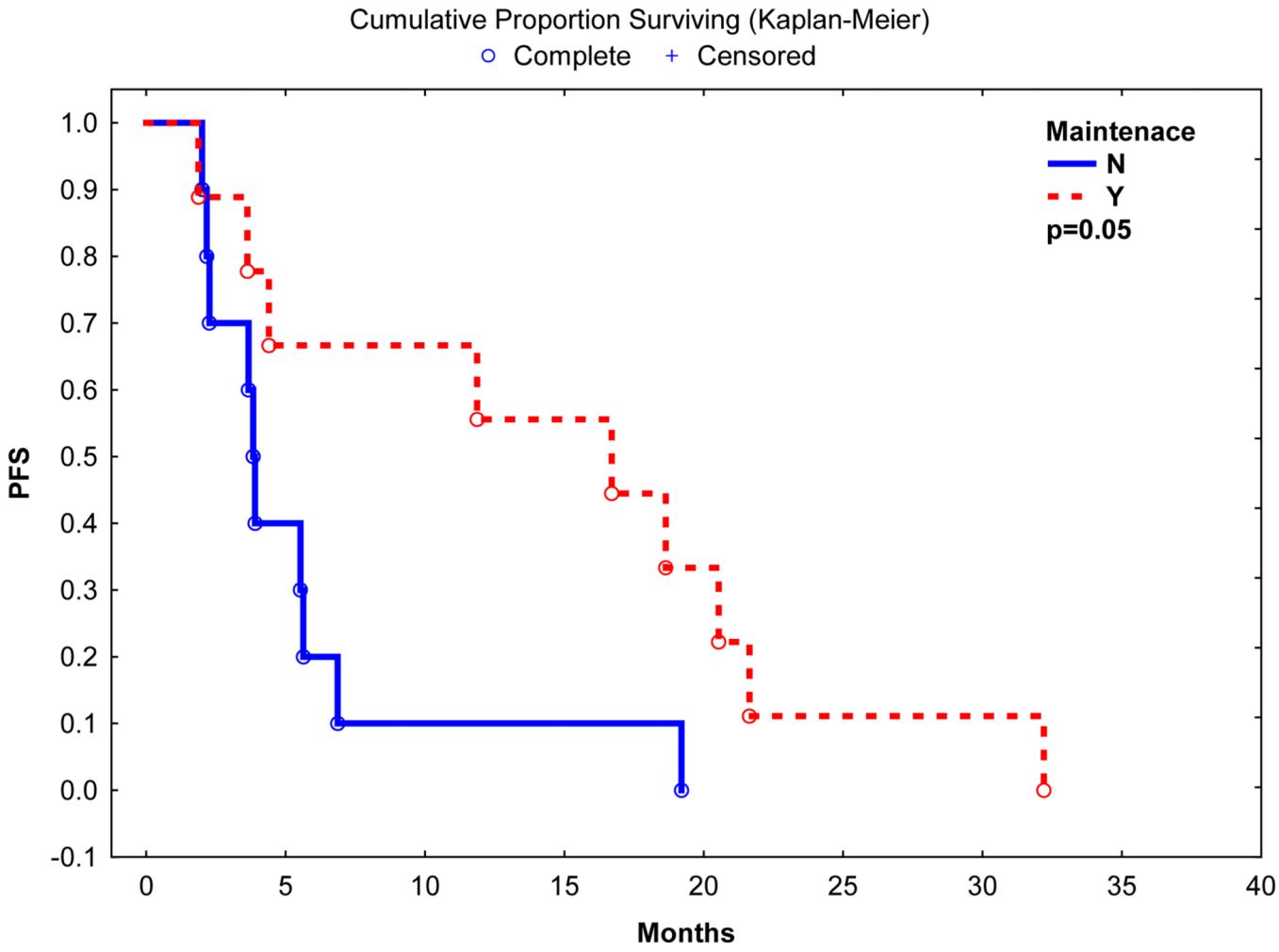

Figure 1:

Progression Free Survival post Autologous Transplant

Median Progression Free Survival: 16.9 vs 3.9 months

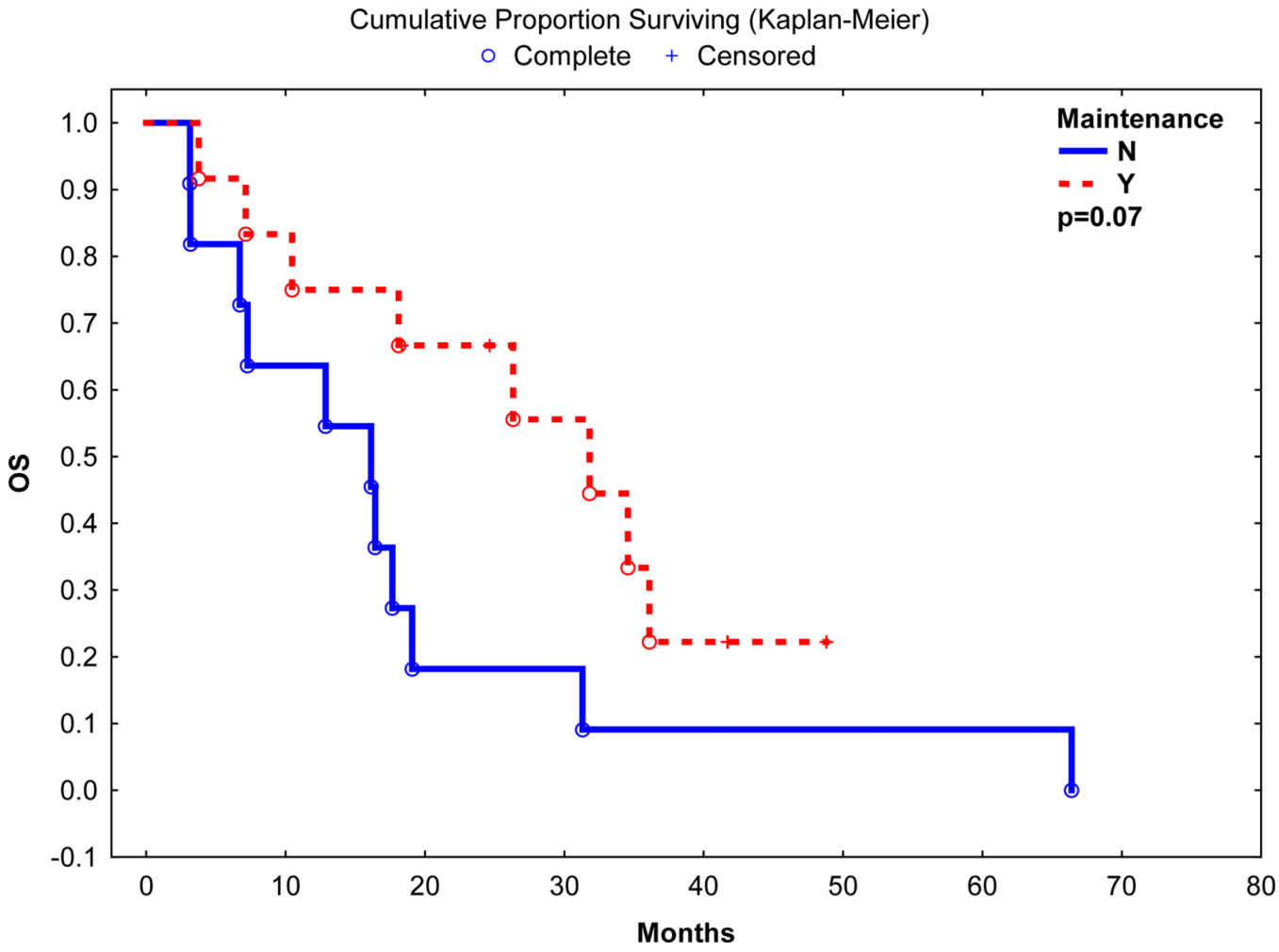

Figure 2:
Overall Survival post Autologous Transplant
Median Overall Survival 31.8 vs 16.1 months

Table 1:

Patient and Disease Characteristics

	Total
Number of Patients	23
Median age at transplant (Range)	56.5 years (42–71)
Sex	
Male	15 (65.2%)
Female	8 (34.7%)
Light Chain	
Kappa	14 (60.8%)
Lambda	9 (39.2%)
Cytogenetic/FISH Group	
High risk	16 (69.5%)
Standard risk	7 (30.4%)
International Staging System	
Stage 1	1(4.3%)
Stage 2	2 (8.6%)
Stage 3	14 (60.8%)
Unknown	6 (26%)
Disease status pre-transplant	
CR/sCR	3 (13%)
nCR	3 (13%)
VGPR	4 (17.3%)
PR	5 (21.7%)
Stable disease/Minimal	3 (13%)
Progression/Relapse	5 (21.7%)

Abbreviations: FISH- Fluorescence in situ hybridization, CR- Complete Response, sCR- stringent Complete Response, nCR- near Complete Response, VGPR- Very Good Partial Response, PR- Partial Response

Table 2:

Maintenance Drug(s) Use Post-Transplant

Total (n-23)	
	Maintenance (n)
Proteasome Inhibitor (PI)	1
Immunomodulatory Drugs (IMiD)	5
PI + IMiD	6
None	11