*British Journal of Pharmaceutical Research*
*13(5): 1-12, 2016, Article no.BJPR.27969*
*ISSN: 2231-2919, NLM ID: 101631759*

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# Post Autologous Stem Cell Transplantation Maintenance for Multiple Myeloma Patients: Real World Experience and Results

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Author MB helped design the study, wrote the protocol, collected data and wrote the first draft of the manuscript. Author YD assisted in the statistical analysis. Author JN helped in summarizing and organizing the data. Author MC was the main statistician who helped in designing the study and supervised all data analysis. Author JSM initiated the study idea, helped in collecting, organizing and analyzing the data, edited the manuscript into its final version. All authors read and approved the final manuscript.*

***Article Information***

DOI: 10.9734/BJPR/2016/27969
Editor(s):
(1) Rahul S. Khupse, Pharmaceutical Sciences, University of Findlay, USA.
(2) Ke-He Ruan, Director of the Center for Experimental Therapeutics and Pharmacoinformatics (CETP) Professor of Medicinal Chemistry & Pharmacology, Department of Pharmacological and Pharmaceutical Sciences, University of Houston, USA.
Reviewers:
(1) Burak Uz, Gazi University, Turkey.
(2) Giampaolo Talamo, Penn State Hershey Medical Center Hershey, PA, USA.
(3) Gokhan Sargin, Adnan Menderes University Medical Faculty, Aydin, Turkey.
Complete Peer review History: http://www.sciencedomain.org/review-history/16650

***Original Research Article***

***Received 28th June 2016***
***Accepted 16th August 2016***
***Published 25th October 2016***

## ABSTRACT

Maintenance therapy is routinely prescribed for multiple myeloma (MM) patients after autologous stem cell transplantation (ASCT). In this retrospective analysis, we evaluated 257 post-ASCT MM patients and compared the effect of various maintenance therapies used in our institution. These include cyclophosphamide (Cy), interferon alpha ± steroids (IST), immunomodulatory drugs (IMiDs) and proteasome inhibitors. Comparisons between maintenance groups in the first (post-

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ASCT) and second line (post-salvage) setting demonstrate no significant differences in progression free survival (PFS) with the exception of IMiDs. These agents, when utilized in the first line maintenance setting, resulted in superior PFS and OS compared to IST (p= 0.0031 and 0.029, respectively) and no maintenance therapy (p= 0.009 and 0.035, respectively). Surprisingly, in the second line maintenance therapy Cy use was associated with a trend favoring improved PFS compared to IMiDs, IFN ± steroids (IST) and bortezomib (Bor) maintenance. Overall survival comparisons demonstrate equivalence between Cy and IST or Bor maintenance groups. Our study confirms advantage of IMiDs as post ASCT maintenance, while the data show that Cy maintenance can be a good alternative in patients who are intolerant or cannot afford IMiDs maintenance, both in first and second line maintenance.

*Keywords: Multiple myeloma; maintenance therapy; novel drugs; cyclophosphamide; autologous stem cell transplantation.*

## ABBREVIATIONS

*ASCT : Autologous stem cell transplantation*
*B2M : Beta-2 microglobulin*
*CR : Complete response*
*Cy : Cyclophosphamide*
*DS : Durie-Salmon*
*IMiDs : Immunomodulatory drugs*
*IST : Interferon and/or steroids therapy*
*MM : Multiple Myeloma*
*OS : Overall survival*
*PFS : Progression free survival*
*VGPR : Very good partial response*

## 1. INTRODUCTION

Recent therapeutic advances have extended the survival for multiple myeloma (MM) patients. In spite of these improvements in progression free survival (PFS) and overall survival (OS), high-dose chemotherapy with autologous stem cell transplant (ASCT) remains a mainstay of treatment and is considered the standard of care for most patients [1-3]. With this approach, complete response rates range from 30-50% and remissions can exceed two years in the absence of additional therapy [4]. The number of long-term remissions remains small.

Two studies from 2012 demonstrated a PFS benefit when MM patients are treated with lenalidomide maintenance therapy after ASCT. Although the data on OS is mixed, lenalidomide maintenance has become widely used, particularly in cases of high-risk disease [3,5-7]. These benefits, however, come at a cost. Lenalidomide maintenance therapy increases healthcare expenditures and a significant proportion of patients develop grade ≥3 toxicity, which may compromise their quality of life [5]. Further underscoring the challenges of lenalidomide maintenance, 6.9-8% of these patients develop secondary neoplasms [5,8,9]. In spite of these challenges, clinicians still prescribe lenalidomide maintenance due, in large part, to the paucity of data available to support the use of other agents. Identifying a well-tolerated maintenance strategy that maintains the efficacy of lenalidomide is highly desirable.

At our institution, we selectively offer cyclophosphamide (Cy) maintenance therapy to MM patients who are intolerant and/or resistant to immunomodulatory drugs (IMiDs), have limited financial resources, or when oral therapy is the preferred route. We retrospectively evaluated our experience with non-IMiD maintenance therapies in order to better understand their toxicities, impact on PFS, and OS. Importantly, the patient population described in this analysis is uniquely different from the carefully selected patients that are enrolled in prospective trials, and provides an important perspective. Our findings demonstrate that post-ASCT Cy maintenance results in comparable PFS and OS in the first and second line setting. However, the use of IMiDs maintenance (mainly lenalidomide) can significantly improve PFS and OS in comparison to all other maintenance drugs evaluated in this analysis. Further, we demonstrate for the first time that Cy is a safe and effective post-ASCT maintenance option for MM patients, and that it is a viable alternative maintenance strategy for selected MM patients.

## 2. PATIENTS AND METHODS

In this single institution, retrospective study we compared the tolerability and efficacy of first and second line maintenance therapies, including Cy maintenance. The study was approved by our Institutional Review Board (protocol No. 138-2012) prior to initiating any data collection. To identify the patient cohort, we queried the

University of Florida Health Center billing database for patients with active MM that underwent ASCT between January 1, 2000 and December 31, 2010. Patients that were lost to follow-up less than six months after ASCT were excluded from this analysis. The second line maintenance analysis was limited to patients that received maintenance therapy after salvage chemotherapy.

Post-ASCT maintenance therapy was selected at the discretion of the attending physician based upon a variety of factors including depth of response after ASCT and clinical trial availability. For analysis, patients were divided into groups based upon the maintenance therapy used. IMiDs, interferon/prednisone (collectively IST), and bortezomib (Bor) were dosed based upon published literature. Patients who could not tolerate or afford other traditional maintenance therapy were treated with Cy. Patients preferentially received Cy 200 mg orally daily for 10 days every four weeks. This Cy dose and length of treatment was selected based on prior published regimens containing this Cy regimen [10]. On rare occasions when intravenous therapy was necessary, Cy was dosed at 750 $mg/m^2$ intravenously every 21 days. In some patients, steroids were co-administered with Cy maintenance therapy. Patients with renal impairment did not need any adjustment in dose of Cy.

At first relapse, patients were offered salvage therapy consistent with our institutional practices and based on attending physician and patient preferences. It is our practice that all relapsed patients receive second line maintenance therapy after an adequate response was achieved. These patients were again divided into groups based upon which maintenance agent was selected. Several patients did not receive second-line maintenance therapy for reasons including salvage ASCT, poor performance status, and patient/provider patient preference. Due to the heterogeneity of this group, we elected not to incorporate a second-line observation group into this analysis.

Response assessments were made in accordance with the International Myeloma Working Group Uniform Response Criteria [11]. After the initiation of maintenance therapy, an attending physician at our institution followed all patients at routine intervals. Patients that received care at practices outside of our institution had their lab values, including MM markers, regularly submitted for review by our medical staff and disease status was documented, when applicable, in the patients' medical records.

For the purposes of this study, we define poor tolerability as one or more dose reductions, or drug discontinuation, resulting from drug toxicity or intolerance. Secondary malignancies are reported as cancers discovered more than six months after the diagnosis of MM. PFS is defined as the time from the start of induction/salvage therapy until documented relapse. PFS data were censored at the last documented clinic visit in all patients that were lost to follow-up more than six months after ASCT. Overall survival is reported as the time period from diagnosis until patient death from any cause. Patient mortality data were obtained from our clinical trials office and confirmed with the social security death index.

PFS and OS calculations were undertaken using the log rank test. P values $<0.05$ are reported as significant. Descriptive statistics are used to describe differences between therapies and the incidence of secondary malignancies in each group.

## 3. RESULTS

### 3.1 Patient Characteristics

A total of 286 patients with active MM underwent ASCT from January 2000 through December 2010 at our institution. In total, 29 patients were excluded; eight were omitted from analysis due to insufficient follow-up and the remaining 21 were excluded because they underwent allogeneic stem cell transplantation during their treatment course [12]. The analysis was completed by June 2015.

Thirty six patients received a second (tandem) ASCT during enrollment in a clinical trial [13]. Conditioning for ASCT consisted of busulfan, cyclophosphamide, and etoposide [14], cyclophosphamide/low dose total body irradiation (given only for second ASCT) [15], or single agent melphalan consistent with our institutional practices at the time of ASCT.

Of the remaining 257 patients, the mean age was 57.4 years and 55.6% of patients were male. Most patients (56.8%) had an IgG paraprotein (Table 1). 169 patients (65.7%) had Durie-Salmon (DS) stage 3A/3B, 69 patients (26.9%) had DS stage 2A/2B, and 19 patients (7.4%) had

DS stage 1A/1B disease. The International Staging System was not used due to limitations in the available diagnostic data. The mean beta-2 microglobulin (B2M) was 5.0 mg/L (range, 0.9-49.1 mg/L) and mean albumin was 3.5 gr/dl (range: 1.6-4.8 gr/dL). At the time of diagnosis, 20.2% of patients had renal involvement, defined as serum creatinine elevation of ≥0.5 mg/dL above the patient's baseline that was not attributable to another cause. Prior to ASCT, 168 patients (65.4%) were treated with one line, 61 patients (23.7%) received two lines, and 28 patients (10.9%) were treated with ≥3 lines of induction therapy. At the time of ASCT, 246 patients had chemosensitive disease and 11 patients had a minimal response or disease refractory to all induction therapy. Additional patient characteristics are in described in Table 1. Median duration of follow-up from diagnosis for all patients was 64.0 months with a range of 11.7-353.8 months.

**Table 1. Patient characteristics**

| | |
|---|---|
| Patient, n | 257 |
| Age, mean years (range) | 57.4 (29-75) |
| Gender, Male/Female | 143/114 |
| **Race, n** | |
| African American | 64 |
| Asian | 3 |
| Hispanic | 12 |
| Caucasian | 175 |
| Other | 3 |
| **Paraprotein type, n** | |
| IgA | 59 |
| IgG | 146 |
| Light Chain only (λ or κ) | 51 |
| Non-secretory | 1 |
| **Durie-Salmon Stage, n** | |
| 1A/1B | 19 |
| 2A/2B | 69 |
| 3A/3B | 169 |
| **Other prognostic features** | |
| Beta-2 Microglobulin >5.5 mg/L, n | 43 out of 163 |
| Albumin < 3.5 g/dL, n | 61 out of 149 |
| Renal Involvement, % of patients | 20.2 |
| **Chemosensitivity, n** | |
| Chemosensitive | 246 |
| Minimal Response | 6 |
| Chemoresistant | 5 |
| **Transplant number** | |
| 1 | 221 |
| >1 | 36 |

## 3.2 First Line Maintenance

In the first line maintenance analysis, 11 patients received Cy, 72 received IST, 75 received IMiDs (45 lenalidomide and 30 thalidomide), and 99 patients did not receive maintenance therapy (observation group). The number of patients with DS stage 3A/3B was equivalent among maintenance therapy groups indicating a comparable disease burden (62.5-68.7%). Patients that went on to receive Cy maintenance therapy had lower rates of CR/VGPR (9.1%) compared to other groups (IST: 47.2%, IMiDs: 65.3%, Observation: 63.6%, p= 0.002). Patients that received Cy maintenance therapy also had a higher incidence of renal dysfunction, however, this difference did not reach statistical significance. Other disease-specific variables, including lines of induction therapy prior to ASCT and chemosensitivity were similar among the groups (Table 2).

There were significant differences in PFS (p= 0.0046, Fig. 1A) and OS (p=0.046, Fig. 1B) between maintenance therapy groups. Treatment with IMiDs maintenance therapy resulted in superior PFS and OS compared to IST (p= 0.0031 and 0.029 respectively; data not shown) and no maintenance therapy (p= 0.009 and 0.035, respectively; data not shown). These findings are consistent with those reported in several prospective randomized trials [5, 6]. Interestingly, head to head comparisons between Cy and the other maintenance formulations show no significant differences in PFS (Fig. 2A-C) or OS (Fig. 2D-F). We identified trends toward improved OS in the Cy group compared to the IST (Fig. 2D) and observation (Fig. 2F) groups. Collectively, in this small dataset, these findings support the use of Cy as an active form of maintenance therapy following ASCT. Furthermore, we believe that further proof for the activity of Cy is the median length of treatment with Cy in this group of 10 patients which was 39.85 months (range, 14.3-331.8).

## 3.3 Second Line Maintenance

Most MM patients, regardless of the maintenance strategy adopted, will relapse and receive additional anti-myeloma therapy. After achieving a satisfactory response, these patients are usually offered maintenance therapy to increase the duration of their remission. We next evaluated the safety and efficacy of the different maintenance regimens in this second line setting.

**Table 2. Comparison of the different maintenance groups post 1st ASCT**

| | Cy | IST | IMiDs | Observation | P-value |
|---|---|---|---|---|---|
| | n=11 | n=72 | n=75 | n=99 | |
| **Durie-salmon stage** | | | | | 0.854 |
| 1A/1B, 2A/2B | 4 | 27 | 26 | 31 | |
| 3A/3B | 7 | 45 | 49 | 68 | |
| **Chemosensitivity** | | | | | 0.519 |
| Sensitive | 10 | 68 | 72 | 96 | |
| Minimal response /Resistant | 1 | 4 | 3 | 3 | |
| **Lines of induction therapy** | | | | | 0.258 |
| 1 | 4 | 51 | 48 | 65 | |
| 2 | 4 | 13 | 18 | 26 | |
| ≥ 3 | 3 | 8 | 9 | 8 | |
| **Response post ASCT** | | | | | 0.002** |
| CR | 0 | 9 | 18 | 29 | |
| VGPR | 1 | 25 | 31 | 34 | |
| PR | 8 | 28 | 20 | 31 | |
| SD/PD | 2 | 9 | 6 | 4 | |
| **Renal involvement** | | | | | 0.170 |
| Yes | 4 | 19 | 12 | 17 | |
| No | 7 | 53 | 63 | 82 | |
| **Patients on hemodialysis** | 0 | 1 | 2 | 1 | NS |
| **Albumin** gr/dl, mean | 3.73 | 3.60 | 3.41 | 3.55 | 0.614 |
| (range) | (3.1-4.3) | (2.0-7.6) | (1.6-4.8) | (2.0-4.8) | |
| **B2M** mg/L, mean | 4.74 | 5.23 | 4.28 | 5.38 | 0.414 |
| (range) | (2.2-13) | (1.4-49.1) | (0.9-20.2) | (1.0-24.8) | |

***Abbreviations:*** *Cy. Cyclophosphamide; IST, Interferon and or steroids; IMiDs, thalidomide or lenalidomide; ASCT, autologous stem cell transplantation; B2M, beta-2 microglobulin; NS, not significant.*

**P values were calculated using the Kruskal-Wallis test while the Fisher exact test was used in all other comparisons.*

***P value was calculated comparing CR/VGPR Vs PR Vs SD/PD*

In total, 74 patients received second line maintenance therapy. These patients are divided into four groups: Cy (21), IST (6), IMiDs (31, [lenalidomide 24, thalidomide 7]), and Bor (16). There are no significant differences in the percentage of DS stage 3A/3B disease (range: 50-68.8%), chemosensitivity, renal dysfunction, or lines of pre-ASCT induction therapy between the groups (Table 3). Patients treated with IST had the highest mean B2M value of 6.19 mg/L, followed by Cy maintenance with a mean of 5.29 mg/L. Patients treated with second line IMiDs maintenance therapy had the lowest mean albumin at diagnosis, compared with patients treated with other maintenance therapies (3.19 vs. 3.6-3.84 gr/dl, p:<0.05).

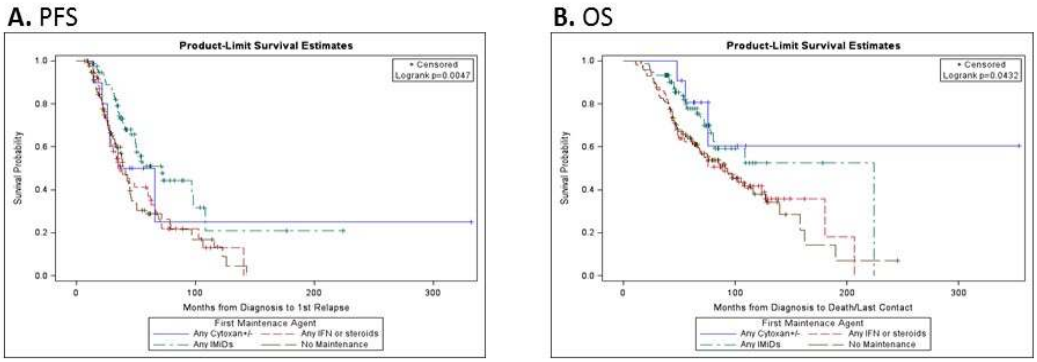
Inter-group comparisons in the second line maintenance setting are in line with our data from the first line setting. Neither the PFS (p= 0.086, Fig. 3A) nor the OS (p= 0.1435, Fig. 3B) comparisons revealed significant differences. Comparisons involving non-Cy maintenance therapy demonstrated a superior OS, but not PFS, benefit with IMiDs maintenance versus IST (140.1 versus 74.1 months, p<0.05, data not shown). There were no significant PFS or OS differences observed between IMiDs and Bor maintenance therapy in the second line setting (data not shown). Once again, head-to-head PFS and OS comparisons between Cy and the other second line maintenance groups were not significantly different (Fig. 4 A-F). A trend favoring improved OS, however, was observed with IMiDs therapy over Cy maintenance (Fig. 4E). Once again, the median length of treatment with Cy in this group of 21 patients was 13.85 months (range, 2.6-66.9). This is, as expected, shorter than the length of Cy treatment in the first line maintenance setting.

### 3.4 Tolerability of Maintenance Therapy

In both the first and second line maintenance setting, Cy has a favorable adverse effect/toxicity profile compared to other forms of maintenance therapy. Patients treated with Cy after ASCT remained on therapy for a median of 22.7 months (range: 3.0-45.3 months) and 13.0 months (range: 1.6-63.9 months) in the first and second line settings, respectively. These patients required fewer dose reductions and discontinued therapy less frequently than patients receiving alternate forms of maintenance. Cy was dose-reduced or discontinued in 18.7% of patients compared to 36% and 34.7% in patients treated with IMiDs and IST, respectively (Fig. 5A). The reasons for dose reduction/ discontinuation in the whole Cy group (n=32) were peripheral blood cytopenias (2) and nausea (1) for a total of 9.4% rate of discontinuation, while the other maintenance groups had multiple side effects that resulted in more frequent treatment discontinuation or changes in drug dose as shown in Table 4. The IMiDs groups (n=106) had 28.3% rate of discontinuation, while the IST groups (n=78) had 25.6% rate of treatment discontinuation.

To evaluate secondary malignancies, we classified malignancies as: non-cutaneous secondary malignancies and total secondary malignancies. Overall, 14/257 (5.5%) patients developed secondary malignancies after the diagnosis of MM, five of which were skin cancers. Two additional patients treated with lenalidomide maintenance were diagnosed with ductal carcinoma in situ of the breast (0.8%) which is considered to be a pre-malignant condition (Table 5). Finally, five patients had a history of malignancy (three female breast cancers and two prostate cancers) that pre-dated their MM diagnosis. Importantly, none of our study patients received radiation prior to transplant and first maintenance.

Of the secondary malignancies, one patient treated with first line Cy maintenance developed a squamous cell carcinoma of the skin that was managed with resection alone. There were four (5.3%) total secondary cancers in the first line IMiDs maintenance therapy group, two (2.7%) of which were non-cutaneous malignancies. We observed six (8.3%) total malignancies, five (6.9%) of which were non-cutaneous in patients treated with first line IST maintenance. Finally,




| 1st Maint. Agent | Median PFS (mos) | 95% Confidence Interval | |
|---|---|---|---|
| Cy | 50.5 | 14.3 | * |
| IST | 37.2 | 29.0 | 60.4 |
| IMiDs | 72.2 | 49.3 | 98.2 |
| Observation | 39.1 | 32.6 | 45.3 |

| 1st Maint. Agent | Median OS (mos) | 95% Confidence Interval | |
|---|---|---|---|
| Cy | Not Reached | 55.3 | * |
| IST | 88.6 | 29.0 | 60.4 |
| IMiDs | 224.4 | 80.6 | 224.4 |
| Observation | 91.5 | 67 | 127.6 |

* Cannot calculate median, curves do not intersect.

**Fig. 1. PFS and OS comparisons between first line maintenance therapy groups reveal significant differences**

*(A) Kaplan-Meier curves comparing PFS between groups demonstrate significant differences between maintenance strategies. (B) There are significant differences in OS between maintenance therapies. Median PFS and OS are depicted in corresponding tables with confidence intervals. Median OS for Cy has not been reached at the time of analysis. P values are inset in each Kaplan-Meier plot*

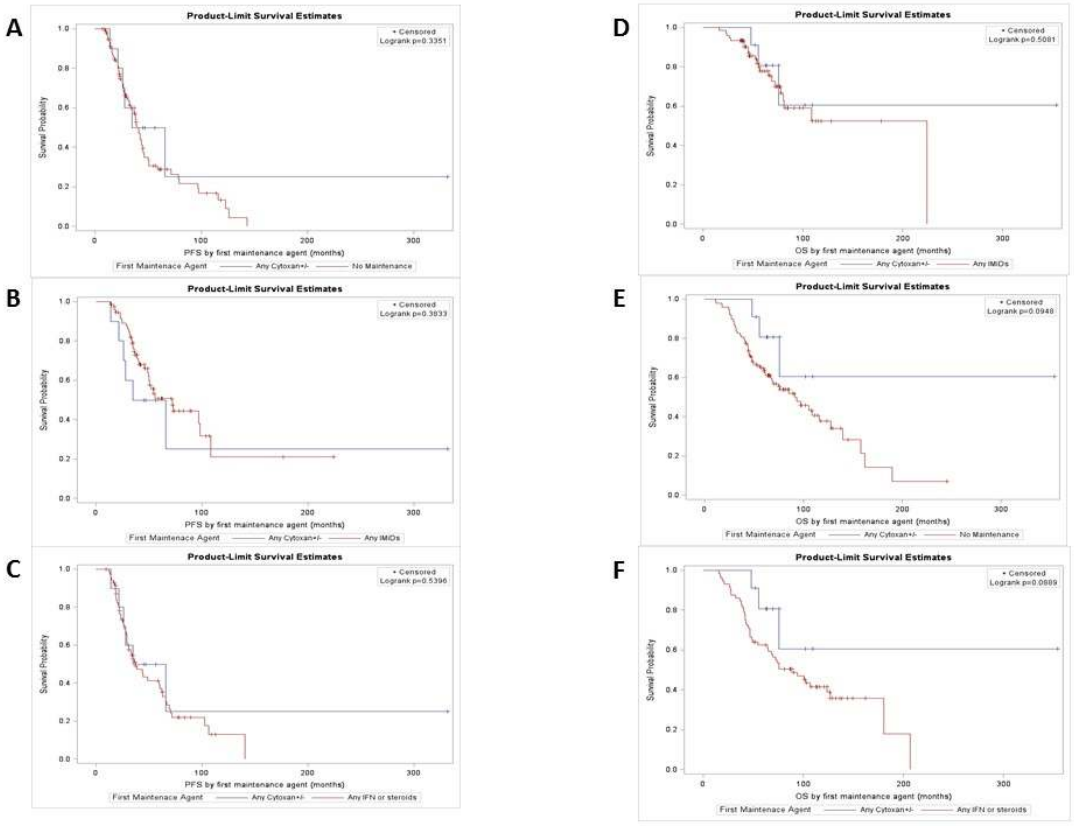



**Fig. 2. Head to head comparison of Cy (+/- steroids) versus other first-line maintenance therapies demonstrates similar PFS and OS**

*(A-C) Treatment with Cy maintenance results in equivalent PFS relative to other maintenance strategies. (D-F) No significant differences were observed in OS between maintenance groups. P values are inset in each Kaplan-Meier plot.*

three (3.1%) patients that were managed with observation in the first line setting developed secondary malignancies, one (1%) of which was cutaneous (Fig. 5B).

## 4. DISCUSSION

In this single institution retrospective study, we report our experience with various MM maintenance therapies, including Cy maintenance, which has not previously been described. Our analysis demonstrates that IMiDs maintenance may be the most effective and provides PFS and OS survival, in comparison to observation or other previously used maintenance therapies. This finding about IMiDs maintenance is consistent with some, but not all, previously published studies [5,6]. Another interesting finding of our study is that Cy is a viable post-ASCT maintenance strategy in the first and second line setting with equivalent PFS and OS compared with other, well-studied post-ASCT maintenance strategies. Indeed, the median length of treatment with Cy in first maintenance setting was comparable to those published for lenalidomide (5) at 39.85 months with a range of 14.3 to 331.7 months. Expectedly, the median length of Cy treatment in the second maintenance setting was much shorter at 13.85 months (range 2.6-66.9), but again comparable to other agents used in the same setting. Furthermore, fewer Cy patients required dose reductions, discontinued therapy, and developed non-cutaneous secondary neoplasms. This study is the first to establish a safe and effective Cy maintenance dose and schedule for MM patients that have achieved a satisfactory response to therapy.

The use of oral Cy maintenance, prescribed in continuous, small doses, has multiple advantages. Cy is preferred over other alkylating

agents, such as melphalan, because it is less myelosuppressive. Cumulative marrow toxicity is rare with Cy and it is therefore believed to have a lower leukemic potential than melphalan [16,17]. The ability to prescribe Cy for up to 10 days, every 4 weeks, may also afford physiologic advantages: First, MM is believed to be a slowly proliferating disease and continuous therapy may better target these growth patterns. Second, this approach may have a metronomic effect via an anti-angiogenic mechanism [18-20]. Third, via inhibitory effects on T regulatory cells, Cy augments immune-mediated anti-myeloma activity [21].

A growing body of evidence supports the use of maintenance therapy in MM patients after ASCT to extend remission duration. To date, the most commonly used maintenance agent is lenalidomide, due in large part to a number of studies demonstrating improved PFS and mixed OS data. Lenalidomide maintenance therapy, however, is associated with additional toxicity and an increased risk of secondary malignancies compared to placebo controls [5,8]. With a cash cost in excess of $160,000 annually, IMiDs maintenance therapy may be financially untenable for uninsured patients in the absence of a clear survival benefit [22,23]. These challenges have prompted clinicians to explore more economical and better-tolerated options for maintenance therapies.

Our study establishes an active dose and frequency for administering Cy maintenance and suggests that it represents an effective and tolerable alternative for post-ASCT maintenance therapy. In first and second line PFS analyses, it performs as well as other maintenance therapies including IMiDs and Bor. Although the PFS appears similar between maintenance agents, Cy maintenance therapy was better tolerated than other forms of maintenance therapy. With an average wholesale price of $7,500 per year, maintenance Cy is a fraction of the price of lenalidomide or Bor [24].

Several limitations of this retrospective study should be considered when interpreting the results: Both the first and second line Cy groups

**Table 3. Comparison of the maintenance groups in the 2nd line setting**

| | Cy | IST | IMiDs | Vel | P-value |
|---|---|---|---|---|---|
| | n=21 | n=6 | n=31 | n=16 | |
| **Durie-Salmon stage** | | | | | 0.854 |
| 1A/1B, 2A/2B | 8 | 3 | 10 | 5 | |
| 3A/3B | 13 | 3 | 21 | 11 | |
| **Chemosensitivity** | | | | | 0.076 |
| Sensitive | 18 | 6 | 31 | 16 | |
| Minimal response / Resistant | 3 | 0 | 0 | 0 | |
| **Lines of Induction therapy** | | | | | 0.998 |
| 1 | 15 | 5 | 20 | 11 | |
| 2 | 4 | 1 | 8 | 4 | |
| ≥ 3 | 2 | 0 | 3 | 1 | |
| **Response Post Reinduction** | | | | | 0.835 |
| CR | 1 | 0 | 2 | 0 | |
| VGPR | 1 | 0 | 2 | 1 | |
| PR | 3 | 1 | 1 | 0 | |
| SD/PD | 0 | 0 | 1 | 0 | |
| Unk | 16 | 5 | 25 | 15 | |
| **Renal Involvement** | | | | | 0.057 |
| Yes | 4 | 3 | 2 | 3 | |
| No | 17 | 3 | 29 | 13 | |
| **Patients on hemodialysis** | 0 | 0 | 0 | 2 | NS |
| **Albumin** gr/dl, mean (range) | 3.73 (2.9-4.5) | 3.6 (3.6-3.6) | 3.19 (2-4.3) | 3.84 (3.2-4.8) | 0.0491* |
| **B2M** mg/L, mean (range) | 5.29 (0.9-20.2) | 6.19 (1.6-9.6) | 3.31 (1.2-1.9) | 4.71 (1.5-8.2) | 0.1932* |

*Abbreviations: See Table 2 footnote. In addition: Vel, Velcade (bortezomib).*P values were calculated using the Kruskal-Wallis test, while all other comparisons were performed using the Fisher exact test*

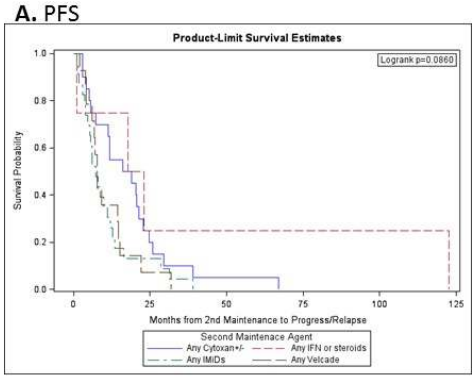
have comparatively small numbers of patients, which may limit the power of statistical comparisons made between the groups. The main reason for the comparatively small number of patients in the Cy groups is our belief that IMiDs are the most effective first-line maintenance agent. This is confirmed in our analysis which showed that IMiDs, especially post ASCT lenalidomide maintenance, resulted in better PFS and OS. Otherwise, OS comparisons are challenging to interpret in MM secondary to disease heterogeneity and variability in induction/salvage regimens. Finally, due to the retrospective nature of this study, the potential for selection bias exists as maintenance therapy decisions are made by their healthcare practitioners, however it still reflects real world practice and experience. On the other hand, we worked to address this concern by comparing disease characteristics between the groups.

In aggregate, these findings indicate that Cy maintenance therapy may represent an effective, well-tolerated, and economically appealing alternative to traditional, established frontline post-ASCT lenalidomide maintenance. Further study, including a randomized trial, may be necessary but is unlikely to occur due to current funding practices. In the absence of this prospective data, we propose that Cy can be considered when other maintenance options are poorly tolerated, unaffordable, or otherwise unavailable.

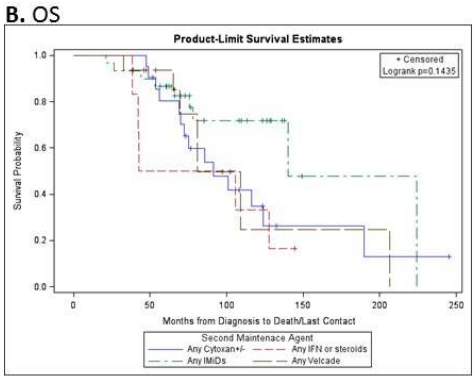
**Table 4. Distribution of number of adverse events causing drug discontinuation or drug dose adjustment that were associated with the post-ASCT maintenance therapies**

| AEs | IST n=78 | IMiDs n=106 | CY n=32 |
|---|---|---|---|
| Cytopenias | 4 | 10 | 2 |
| Transaminitis | 4 | 1 | 0 |
| Flu like symptoms /fever | 5 | 0 | 0 |
| Nausea | 0 | 3 | 1 |
| Diarrhea | 0 | 2 | 0 |
| Cholecystitis | 1 | 0 | 0 |
| Peripheral neuropathy | 0 | 5 | 0 |
| Fatigue | 2 | 2 | 0 |
| Rash | 2 | 0 | 0 |
| Acute kidney injury | 0 | 1 | 0 |
| Tremor | 0 | 1 | 0 |
| TTP* | 1 | 0 | 0 |
| Syncope | 0 | 1 | 0 |
| Thrombosis | 0 | 1 | 0 |
| Unknown | 1 | 3 | 0 |

**TTP: thrombotic thrombocytopenic purpura*




| Maint. Agent | Median PFS (mos) | 95% Confidence Interval | |
|---|---|---|---|
| Cy | 17.5 | 5.5 | 22.7 |
| IST | 20.3 | 0.9 | 122.7 |
| IMiDs | 7.1 | 4.6 | 11.0 |
| Vel | 7.6 | 4.0 | 14.7 |




| Maint. Agent | Median OS (mos) | 95% Confidence Interval | |
|---|---|---|---|
| Cy | 91.5 | 69.7 | 123.9 |
| IST | 74.1 | 38.2 | * |
| IMiDs | 140.1 | 77.8 | 224.4 |
| Vel | 80.8 | 69.2 | 206.7 |

* Cannot calculate.

**Fig. 3. Second line Cy maintenance therapy results in similar PFS and OS compared to other maintenance agents**

*(A) Group comparisons between the four maintenance groups in the 2nd line maintenance cohort do not demonstrate significant PFS differences. (B). There are no significant OS differences between groups. P values are inset in each Kaplan-Meier plot*

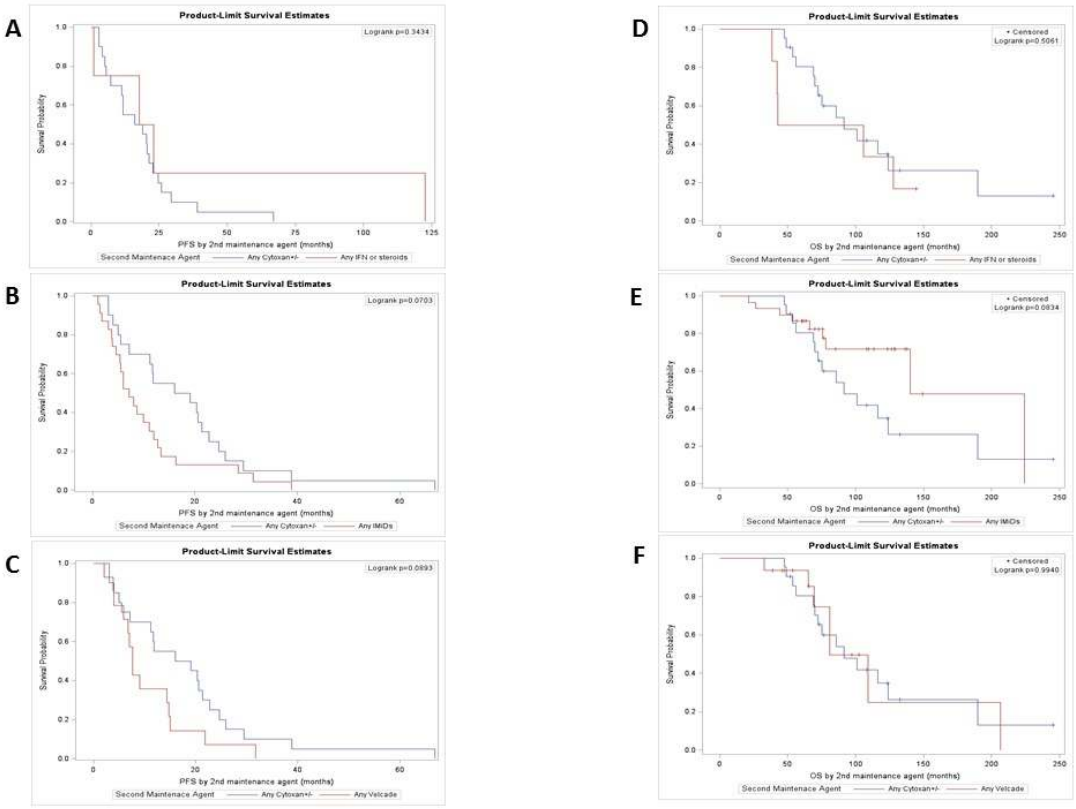



**Fig. 4. Head to head comparisons between Cy and other second line maintenance therapies reveal similar PFS and OS**

*(A-C) There are no significant PFS differences observed between groups in the second line maintenance setting. (D-F) OS comparisons between 2nd line Cy (+/- steroids) maintenance versus other maintenance therapies do not reveal significant differences. P values are inset in each Kaplan-Meier plot*

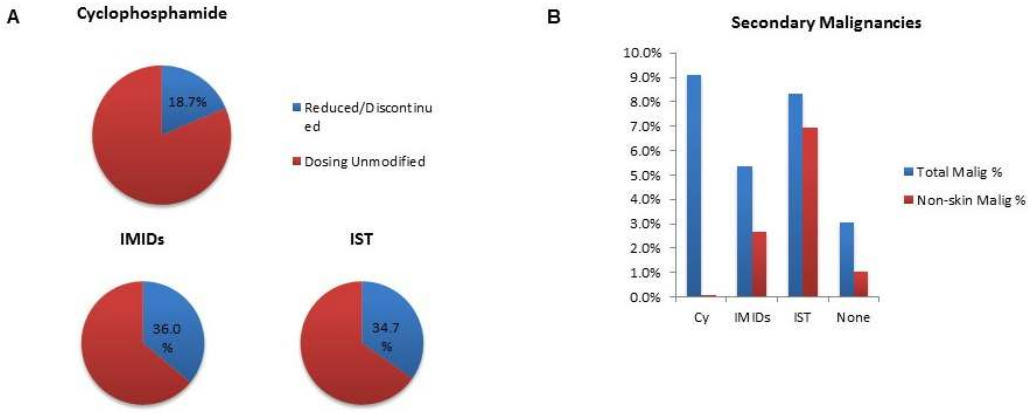



**Fig. 5. Cy maintenance therapy is well tolerated with fewer dose reductions and secondary malignancies**

*(A) Maintenance therapy was interrupted or the dose was reduced less frequently with Cy (18.7% of patients) compared to IMiDs (36%) and IST (34.7%) therapy. (B) Patients that received first line Cy maintenance had the fewest non-cutaneous malignancies (0%) compared with other forms of maintenance therapy*

**Table 5. Secondary malignancies and association with type of maintenance**

| Patient | Maint #1 | Maint #2 | Malignancy type |
|---|---|---|---|
| 1 | IMiDs | None | Adenocarcinoma (appendix) |
| 2 | IMiDs | Bortezomib | Breast |
| 3 | IST | None | MDS |
| 4 | IST | None | Acute myeloid leukemia |
| 5 | IST | None | Prostate |
| 6 | IST | IST | Non-small cell lung |
| 7 | IST | Bortezomib | Breast |
| 8 | None | None | Breast |
| 9 | None | IMiD | Papillary carcinoma |
| 10 | Cy | Bortezomib | Squamous cell (skin) |
| 11 | IMiDs | None | Squamous cell (skin) |
| 12 | IMiDs | None | Squamous cell (skin) |
| 13 | IST | IMiD | Squamous cell (skin) |
| 14 | None | None | Basal cell (skin) |
| 15 | IMiDs | None | DCIS |
| 16 | IMiDs | None | DCIS |

***Abbreviations:*** *DCIS, ductal carcinoma in situ*

## 5. CONCLUSIONS

Our study results lead to few conclusions. First, our study shows that the use of IMiDs maintenance post ASCT, mainly lenalidomide, results in significant increase in PFS and OS. Second, Cy maintenance can be effective alternative with potentially less significant side effects, both in the period after ASCT and later in patients who relapse post ASCT. Third, the use of 10-days course of oral Cy is convenient and effective and should be adopted as an alternative when other maintenance options are poorly tolerated, unaffordable, or otherwise unavailable.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

This study was approved by our Institutional Board Review as a retrospective chart review study (protocol No. 138-2012).

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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