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Cyclophosphamide, Thalidomide and Dexamethasone (CTD) as First-Line Therapy in Multiple Myeloma Patients: An Experience in a Clinical Haematology Centre in Dakar, Senegal

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Abstract

Introduction: Induction therapy followed by high-dose chemotherapy with autologous stem cell transplantation remains the gold standard for myeloma patients who can tolerate this treatment approach. In a developing country setting, in the absence of availability of bone marrow transplantation, the CTD protocol is an accessible treatment regimen whose efficacy and lower toxicity compared to the Melphalan Prednisone protocol has been reported. This protocol has been administered since 2018 in first line. It's against this backdrop we perform this study to assess the efficacy of this CTD protocol in first line therapy. **Methods:** We conducted a descriptive and analytical study including clinical, paraclinical and evolutionary data of 50 patients with MM treated during the period range from 01 September 2018 and 01 July 2022 with the CTD protocol of cyclophosphamide (500 mg at D1, D8 and D15), dexamethasone (40 mg weekly) and thalidomide (100 mg/day) in 28-day cycles. Survival outcomes were estimated by the Kaplan-Meier method. **Results:** The mean age was 62.3 ± 9.1 years and the sex ratio was 0.7. An advanced prognostic score at diagnosis was found in 73.5% of patients according to the Salmon and Durie score and in 32% according to the ISS. Overall remission was noted in 64%, of which 34% were in very good partial remission and partial remission in 12% of cases. Progression was noted in 4 patients. Treatment-related side effects were mainly peripheral neuropathy and anaemia in 3 patients respectively. The median survival was 38.4 months. The progression-free survival was 60%. An advanced age (≥65 years) is correlated with negative impact on survival ($p = 0.04$). **Conclusion:** Cyclophosphamide, thalidomide and dexamethasone give good outcome with less toxicity. Thus, it remains a first-line treatment alternative for newly diagnosed and low-income patients.

Keywords

Myeloma, Chemotherapy, Survival

1. Introduction

Multiple myeloma is an incurable haematological malignancy despite numerous advances. Its prevalence is 176,404 cases of all cancers in 2020 worldwide with a mortality of 117,077 cases in the same year [1]. Its diagnosis is based on the International Myeloma Working Group (IMWG) criteria [2].

High-dose therapy and autologous stem cell transplantation (ASCT) remain the gold standard therapy approach [3]; with progression-free survival and overall survival higher than those treated with conventional therapies [4]. In sub-Saharan Africa, the management of MM has been based for years on conventional chemotherapy using the MP protocol; innovative therapies for MM were not widely available [5].

The combination of cyclophosphamide, thalidomide and dexamethasone (CTD) has been proven to be effective and less toxic than the Melphalan Prednisone protocol [6]. It is indicated for induction before high-dose therapy and GSCA [7]. This protocol has been implemented in our patients since 2018 based on its financial accessibility in a developing country setting. The evaluation of this protocol was necessary. It's against this backdrop we conducted this work, with a main objective of assessing the efficacy of the CTD protocol as a first-line treatment in patients followed for newly diagnosed multiple myeloma.

2. Methods

We conducted a descriptive and analytical study over a 47-month period from 01 September 2018 to 01 July 2022 at the clinical haematology department of Dalal Jamm Hospital in Dakar. All patients diagnosed with multiple myeloma according to the IMWG 2014 criteria [3] and receiving the CTD protocol in first line were included. Prognostic data were assessed with Durie and Salmon and ISS prognostic classifications. Treatment evaluation was performed at the end of treatment.

Treatment was implemented according to the following schedule: Cyclophosphamide (500 mg at D1, D8 and D15), Dexamethasone (40 mg: D1, D8, D15 and D22) and Thalidomide (100 mg/day continuous daily).

Responsive treatment was defined according to the International Myeloma Working Group (IMWG) standards. Efficacy assessment of all patients was scaled as complete remission (CR), very good partial remission (VGPR), partial remission (PR) and minimal remission (MR), stable disease (SD) and disease progression (DP).

Adverse effects were also studied.

Survival variables were set by the method ("overall survival" OS), and the event was death from any cause. Follow-up time was from the date of diagnosis

to the end of the study for overall survival. Progression-free survival (PFS) was studied. PFS was defined as the time from the date of inclusion to documented progression or death; progression was defined as relapse after a complete response (CR) if the patient had achieved a CR, or progressive disease if the patient had not achieved a CR. The graphs were presented as Kaplan-Meier pattern with median survival. The log rank test of comparison was used with a threshold of $p < 0.05$.

Ethical aspects

We discussed every medical record on a therapy decision-making comity prior to the treatment onset and the patient was given all available therapeutic alternatives with their costs, benefits, side effects and availability of products. An informed consent form was then signed.

Statistical study

The data were entered using the Sphinx software version 5.1.0.2. Data analysis was performed with SPSS (Statistical Package for Social Sciences) version 18. The Kaplan Meier survival graph was used to assess the probability of survival of patients. The comparison of the survival probabilities between the different groups was done using the log rank test with a significance level of $p < 0.05$.

3. Results

Over a 47-month period, 50 patients were included, including 22 men and 28 women, with a sex ratio of 0.7. The mean age of our patients was 62.3 ± 9.1 years. Patients under 65 years of age represented 70% of the study population (n = 35). The clinical and biological characteristics of the patients are summarised in Table 1 and Table 2 respectively.

The initial prognosis assessment showed that 32% of the patients were classified as ISS stage III and 95.5% of the cases as Durie and Salmon stage III. The different prognosis stages are summarised in Table 3.

Treatment-related adverse effects were mainly peripheral neuropathy and

Table 1. Clinical data on admission.

Symptoms on admission	Frequency	Percentage (%)
Bone pain	39	78
Anaemic syndrome	28	56
Plasmocytoma	3	6
Root compression	6	12
Spinal cord compression	9	18
Ponytail syndrome	2	4
Infections	15	30
Pathological fractures	6	12
Malignant hypercalcaemia	4	8

anaemia in 3 patients respectively. No cases of thrombosis were noted.

The evolution of the treatment resulted in an overall remission of 64% of which 6% were in complete immunophenotypic remission, 2% in complete remission, 38% in very good partial remission and partial remission in 12% of cases. Progression was noted in 8% of cases and mortality accounted for 22.4% of cases.

Overall survival was at 38.4% at 47 months (Figure 1) while the median

Table 2. Biological abnormalities on admission.

Parameters	Frequency	Percentage (%)
Anemia (g/dL)	44	88
Thrombocytopenia (G/L)	7	14
Leukopenia (G/L)	4	8
Hypercalcemia	14	28
Hypoalbuminemia	33	66
Pu > 150 mg/24h	13	26
CRP > 6 mg/L	15	30

Table 3. Prognosis score at diagnosis.

Prognostic stage		I	II	III	A	B
Durie and Salmon (n = 50)	n		2	46	41	7
	(%)		4	95	85	14
ISS (n = 25)	n	3	7	8		
	(%)	1.7	38.9	44.4		

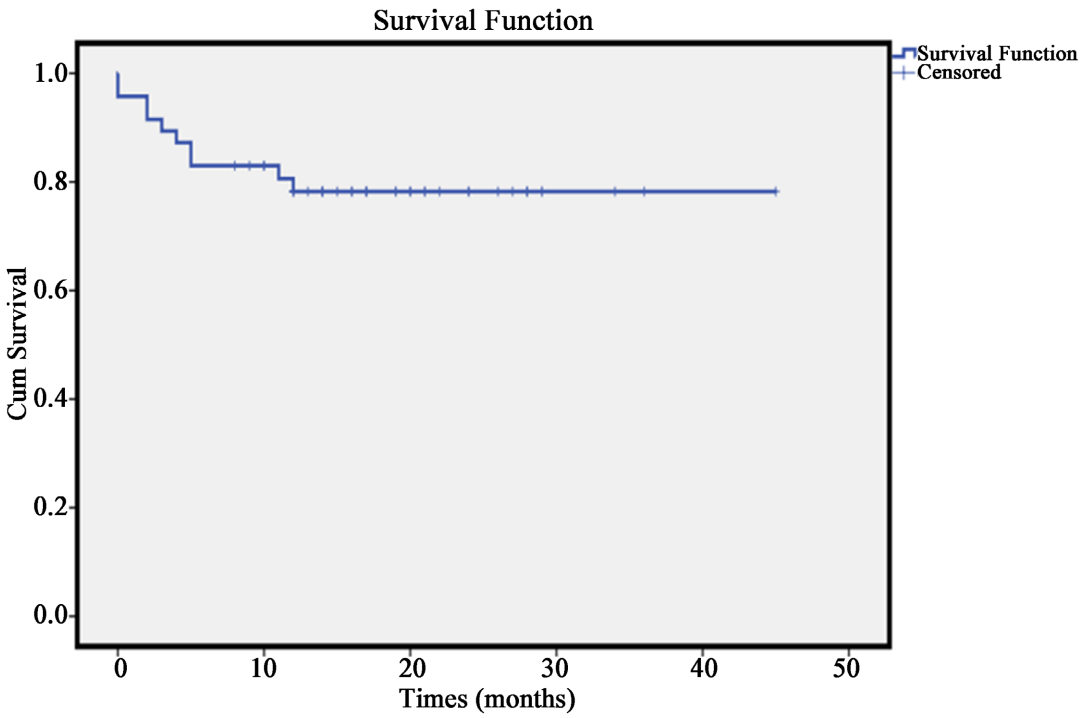

Figure 1. Overall survival.

progression-free survival was at 60% (Figure 2). Regarding survival by age (Figure 3), the overall survival of patients under 65 years of age was 85% while

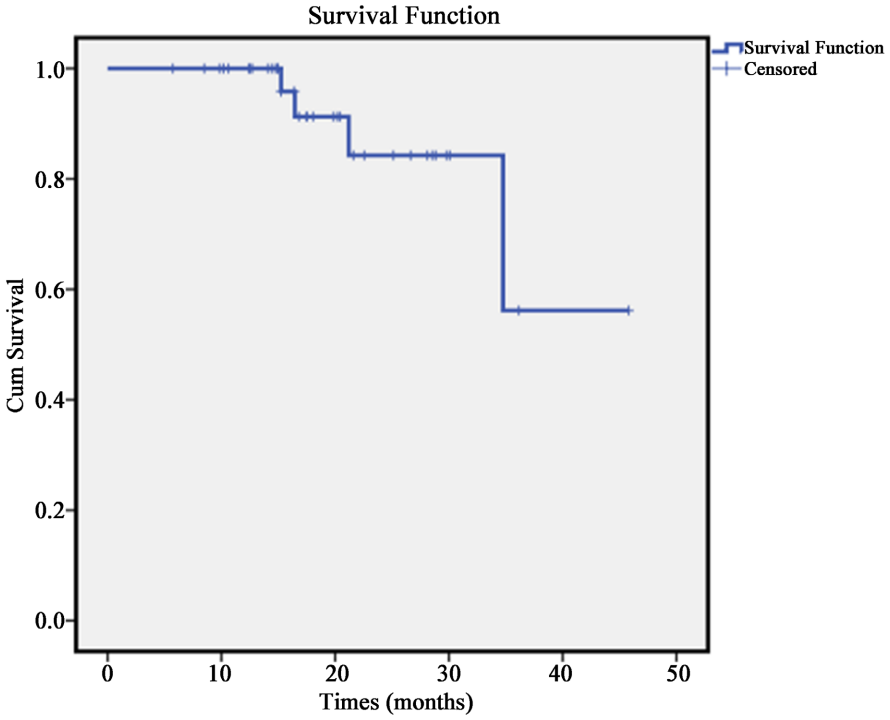

Figure 2. Progression-free survival.

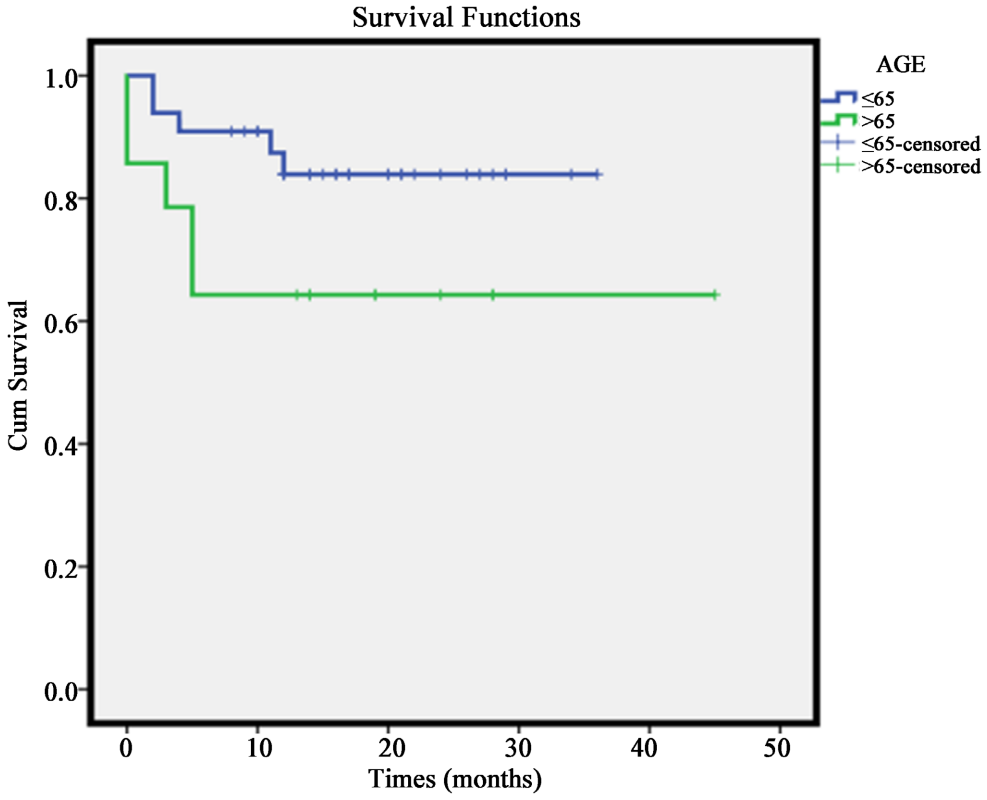

Figure 3. Survival by age.

that of patients aged 65 years and over was 63% with a significant difference in survival between these two populations (p = 0.04).

4. Discussion

Multiple myeloma therapy in sub-Saharan Africa, and more particularly in Senegal, is hampered by the unavailability of bone marrow transplant and the inaccessibility of innovative therapy due to their high cost. The CTD combination is an accessible treatment regimen in our setting. The efficacy of this protocol has been evaluated in several studies. Indeed, in China, a retrospective analysis of 49 cases by Gu Y *et al.* [8] evaluated the efficacy and safety of CTD regimens in the treatment of patients with newly diagnosed multiple myeloma and found an overall complete remission of 65.3%. In a low- and middle-income country setting, Vasquez *et al.* [9] found an overall response of 69.5% over a period of 81 months. In our study, this remission was 64% of cases. The superiority of the CTD protocol over the MP protocol was proven by Morgan *et al.* [6] in their study of the CTD protocol as initial treatment for multiple myeloma patients unsuitable for autologous transplant in 2011, with an overall response rate significantly higher with CTD than with MP (63.8% vs. 32.6%; p < 0.0001). In our study, this protocol allowed us to achieve a complete remission in 2% of cases similar to Vasquez *et al.* [9] (3%) and a very good partial response in 38% of cases higher than those of Gu Y *et al.* [8] (30.6%) and Morgan *et al.* [6] (16.9%).

Besides the efficacy of CTD protocol in newly diagnosed patients as first line therapy, it can be considered as induction therapy for newly diagnosed multiple myeloma patients eligible for stem cell autotransplant. Indeed, Morgan *et al.* [7] in 2012 in a population of 555 patients, noted an overall response rate of 82.5% and a complete response in 13% of cases. This complete response was maintained at 50.0% after autotransplant. Thus, in our patients with transplant plans, this protocol can be used as a first line treatment.

The survival outcome was unremarkable in our study with a median OS of 38.4 months compared to previous studies in our setting where the median survival was 20 months [10]. Our data corroborate with that of Morgan *et al.* [7] where the median follow-up of patients was 44 months and the median PFS was 13 months over a 4 year period. Gu *et al.* [8] found a 70% OS with a median survival of 11.5 months over 26 months (2013-2016). Vasquez *et al.* [9] reported a 3-year OS of 63.4% and a 3-year PFS of 47.4%. In our study we observed a significant impact of age on OS (p = 0.04). This negative impact of advanced age has been reported in several studies. Indeed, Nacera *et al.* [11] reported an overall survival at 93 months of 11% with a median survival of 36 months in subjects less than 65 years of age. Similarly, Morgan *et al.* [7] observed a significant impact of age on OS. The advanced stage at diagnosis in most patients could explain these results in our cohort.

Limitations

The main limitation of our study is the small sample because of a monocentre

series. Another major limitation of the study is the unavailability of cytogenetic and molecular techniques to categorise patients according to the risk.

5. Conclusion

Cyclophosphamide, thalidomide and dexamethasone give good results with less toxicity. It remains a first-line treatment alternative for newly diagnosed patients with low income with an overall survival of 80% at 47 months.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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