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Original article

Evaluation of the therapeutic response in 36 patients followed for myeloma under triple therapy between 2019 and 2021: Single-center study in the clinical hematology department of Dakar University Hospital

Évaluation de la réponse thérapeutique chez 36 patients suivis pour myélome sous trithérapie entre 2019 et 2021 : Etude monocentrique au service d'hématologie clinique du CHU de Dakar

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Résumé

Introduction : La prise en charge du myélome repose essentiellement sur l'association de molécules de classes différentes ; les traitements actuels permettent souvent une réduction drastique voire la disparition de la protéine monoclonale. Le but de cette étude est d'évaluer la réponse thérapeutique des patients sous trithérapie suivis au service d'hématologie clinique du CHU de Dakar.

Méthodologie : Nous avons réalisé une étude rétrospective portant sur 36 dossiers de patients suivis pour myélome multiple sous trithérapie.

Résultats : Le traitement spécifique de 1ère ligne a été : le MPT chez 15 patients (44,11%) ; CTD chez 15 patients (44,11%) ; les protocoles incluant le bortezomib (VCD, VMP, VTD) chez 6 patients (16,66%). Neuf patients (25%) n'avaient pas de réponse : 3 patients CTD ; 5 patients MPT et 1 patient VTD. Parmi les patients qui étaient sous protocole MPT, 5 patients (33,3%) étaient en réponse partielle ; ceux qui étaient sous protocole CTD avaient capitalisé 9 patients (60%) en réponse partielle à 6 mois de traitement. Les patients ayant reçu dans leur traitement le bortezomib, ont obtenu un taux de réponse partielle de 66,6% soit 4 patients et un taux de très bonne réponse partielle de 33,33 % (2 patients). Le délai moyen de la réponse était de 5,08 mois sous CTD ; 7 mois sous MPT. La durée moyenne de survie sans progression était de 5,2 mois et 4,83 mois pour les patients qui sont respectivement sous MPT, CTD. La survie globale à 3 ans était de 77,7 %.

Conclusion : Notre étude a montré l'efficacité de la trithérapie incluant le bortezomib tant pour l'obtention d'une réponse partielle que pour la durée de la survie sans progression.

Mots-clés : Bortezomib, Trithérapie, CTD, MPT.

Abstract

Introduction: The treatment of myeloma is essentially based on the combination of molecules of different

classes; current treatments often allow a drastic reduction or even disappearance of the monoclonal protein. The aim of this study is to evaluate the therapeutic response of patients receiving triple therapy followed in the clinical hematology department of Dakar University Hospital.

Methodology: We carried out a retrospective study covering 36 files of patients followed for multiple myeloma under triple therapy.

Results: The specific 1st line treatment was: MPT in 15 patients (44.11%); CTD in 15 patients (44.11%); protocols including bortezomib (VCD, VMP, VTD) in 6 patients (16.66%). Nine patients (25%) had no response: 3 CTD patients; 5 MPT patients and 1 VTD patient. Among the patients who were on the MPT protocol, 5 patients (33.3%) were in partial response; those who were on the CTD protocol had capitalized 9 patients (60%) in partial response to 6 months of treatment. Patients who received bortezomib as part of their treatment obtained a partial response rate of 66.6%, i.e. 4 patients, and a very good partial response rate of 33.33% (2 patients). The average time to response was 5.08 months under CTD; 7 months under MPT. The average progression-free survival time was 5.2 months and 4.83 months for patients who were on MPT, CTD, respectively. Overall survival at 3 years was 77.7%.

Conclusion: Our study showed the effectiveness of triple therapy including bortezomib both for obtaining a partial response and for the duration of progression-free survival.

Keywords: Bortezomib, Triple therapy, CTD, MPT.

Introduction

Multiple myeloma (MM) or Kahler's disease is a hematological malignancy characterized by the clonal proliferation of tumor plasma cells that invade the bone marrow and secrete a monoclonal immunoglobulin or a fragment of monoclonal immunoglobulin (free light chain) [5]. It evolves from a clinically silent precancerous stage called monoclonal gammopathy of undetermined significance (MGUS). Over the years, the diagnosis of multiple myeloma has required evidence of target organ damage attributable to the neoplastic plasma cell clone: hypercalcemia, renal failure, anemia, and osteolytic bone lesions, commonly referred to as CRAB features [11]. This definition was conservative and aimed to prevent patients with MGUS and indolent myeloma from receiving unnecessary and toxic chemotherapy. Multiple myeloma is predominantly a male disease, with a mean age at diagnosis of 66 years, and unfortunately remains a disease whose management is currently problematic. However, recent decades have seen advances in understanding the pathophysiology of myeloma, which has led to the development of new therapeutic molecules, improving patients' survival and quality of life [15]. In newly diagnosed multiple myeloma, the combination of lenalidomide, bortezomib and dexamethasone (RVd) is one of the most widely used treatment regimens with a residual disease negativity rate of 35.6%. Anti-CD38 monoclonal antibodies increase efficacy when added to standard of care regimens with a residual disease negativity rate of 50% [4]. In sub-Saharan Africa, there is a problem with the accessibility of innovative drugs [2]. Consequently, the therapeutic results obtained are not the best in the race for optimal management of multiple myeloma. However, more or less satisfactory therapeutic responses are obtained. To our knowledge, few scientific studies have been conducted on the therapeutic results of multiple myeloma in our country. Against this backdrop, we aimed to evaluate the therapeutic response of patients on triple therapy.

Methodology

We carried out a retrospective, descriptive study of analytical purpose in the period ranging from January 2019 to October 2021 (34 months) in the clinical hematology department of the National Blood Transfusion Centre in Dakar. The study was based on

data from the physical medical record of 36 patients followed for multiple myeloma during the study period.

- Patients included: symptomatic multiple myeloma diagnosed according to the 2014 International Myeloma Group (IMWG) criteria [12], followed for at least 6 months and treated with three molecules
- Methods: During the study period, 36 patients met our inclusion criteria.

The main drug combinations used were :

- Mephalan - Prednisone - Thalidomide (MPT),
- Cyclophosphamide - Thalidomide - Dexamethasone (CTD)
- Bortezomib - Thalidomide - Dexamethasone (BTD)
- Bortezomib - Cyclophosphamide - Dexamethasone (BCD)
- Bortezomib - Melphalan - Prednisone (BMP)

Dosage and route of administration

- Mephalan: 0.15 to 0.25 mg/ kg/ day per os from D1 to D4
- Cyclophosphamide: 300 mg/m2/day (500 mg maximum) intravenously on D1-D8-D15
- Thalidomide: 100mg/day per os continuously
- Bortezomib: 1.3 mg/m2/day subcutaneously on D1-D8-D15-D22
- Prednisone: 2 mg/m2 per os from D1 to D4
- Dexamethasone: 40 mg intravenously D1-D8-D15-D22

Criteria for assessing therapeutic response :

The therapeutic response was assessed between the 4th and 8th month of first-line treatment. The types of response obtained were [6]:

- Partial response, defined as at least 50% reduction of the monoclonal component,
- Very good partial response is defined as at least 90% reduction of the monoclonal component
- Complete response: Disappearance of the monoclonal component, with negative immunofixation and bone marrow plasma count < 5%.

The 3-year overall survival of patients was assessed.

Data analysis :

Data entry and statistical analyses (mean, median, standard deviation) were performed in Microsoft Excel.

Ethical considerations

All ethical considerations are taken into account from data collection to publication of the results.

Data collection was carried out with the informed consent of the patients and all necessary information about the content of the study.

Results

In a population of 69 patients followed for multiple myeloma, 36 patients accounting for 52% were on triple therapy. The sex ratio was 3.27 and the mean age was 59.27 years with a standard deviation of 10.24. Five patients were under 50 years of age. Only one patient was exposed to toxic substances, nine patients underwent a comorbidity. The mean time to diagnosis was 8.64 months. The main circumstances of discovery were bone pain (61.1%) and anemia (61.1%) followed by spinal cord compression (30.5%). Renal function impairment was found in 9 patients at diagnosis. Among the patients who underwent immunofixation, the monoclonal component was IgG Kappa in 81.8%, IgG Lambda in 9%, IgA Kappa 1%, IgA Lambda 1% and all light chain myelomas were Kappa (Table 1). Regarding the outcome, 25 patients (69.5%) were classified by ISS and 11 patients (30.5%) by Salmon and Durie (Table 1). The specific 1st line treatment was: MPT in 15 patients (44.1%); CTD in 15 patients (44.1%); BCD in 4 patients (11.1%); BMP in one patient as well as the BTD protocol (Table 1). Among the patients who were on the MPT protocol, 5 patients (33.3%) were in partial response; those on the CTD protocol represented 9 patients (60%) in partial response at 6 months of treatment. Patients treated with bortezomib had a partial response rate of 66.6% (4 patients) and a very good partial response rate of 33.33% (2 patients) (Figure 1). The complete response could not be assessed in our patients since the myelogram to

assess plasma count was not performed systematically. The mean time to response was 4 months with the protocols including bortezomib (BMP, BTD, BCD); 5.08 months with the CTD protocol; 7 months with the MPT protocol (figure 2). The mean duration of progression-free follow-up was 6.6 months for patients on the protocols with bortezomib (BCD, BTD, BMP); 5.2 months and 4.83 months for patients on MPT and CTD, respectively (Figure 2). Eleven patients had disease progression, thus benefiting from a 2nd line protocol: 3 patients on TPM and 9 patients on CTD. The overall survival at 3 years was 77.7%

Table I: Socio-demographic, diagnostic, prognostic and therapeutic data of myeloma patients at Dakar University Hospital (2019 - 2021)

Parameters	Number
Demographic Parameters	**36**
Age : < 60 years / > 60 years	19 (52,7%) / 17 (47,2%)
Gender : M/F	25 (69,4%) / 11 (36,5%)
Circonstances of discovery	**36**
Bone pain	22 (61,1%)
Anemia	22 (61,1%)
Medullar compression	11 (30,5%)
Pathological fractures of the limbs	3 (8,3%)
Infections	1 (2,7%)
Renal function impairment	1 (2,7%)
C.R.A.B criteria	**36**
Hemoglobin < 10 g/dl	31 (86,1%)
Osteolytic lesions	31 (86,1%)
GFR according to CKD Epi < 40 ml/mn	9 (25%)
Adjusted calcemia > 105 mg/l	7 (19,4%)
Serum protein electrophoresis	**36**
Monoclonal pic > 30 g/l	31 (86,1%)
Hypogammaglobulinemia	2 (5,5%)
Serum protein immunofixation	**22**
IgG Kappa	18 (81,8%)
IgG Lambda	2 (9%)
IgA Kappa	1 (4,5%)
Ig A Lambda	1 (4,5%)
Urine protein immunofixation	**2**
Light chain Kappa	2 (100%)
International Staging System (ISS)	**25**
I	0 (0%)
II	9 (36%)
III	16 (64%)
Chemotherapy protocols	**36**
MPT	15 (41,7%)
CTD	15 (41,7%)
BCD	4 (11,1%)
BMP	1 (2,8%)
BTD	1 (2,8%)

N : Total number
% : Percentage
M/F : male / female
GFR: glomerular filtration rate
IgG : immunoglobulin G
IgA : immunoglobulin A

Kappa, Lambda : light chain Osteolytic lesions
C.R.A.B : Calcemia, Renal function, Anemia, ISS : International Staging System

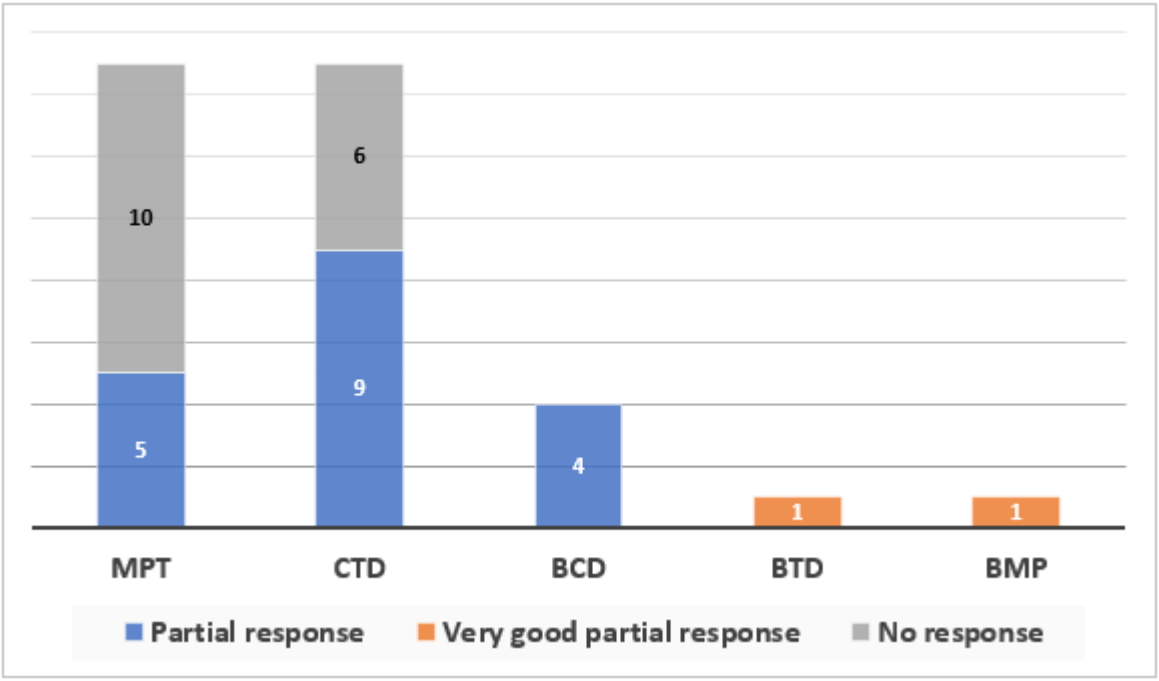


Figure 1: Type of response obtained according to the protocols at 6 months of treatment

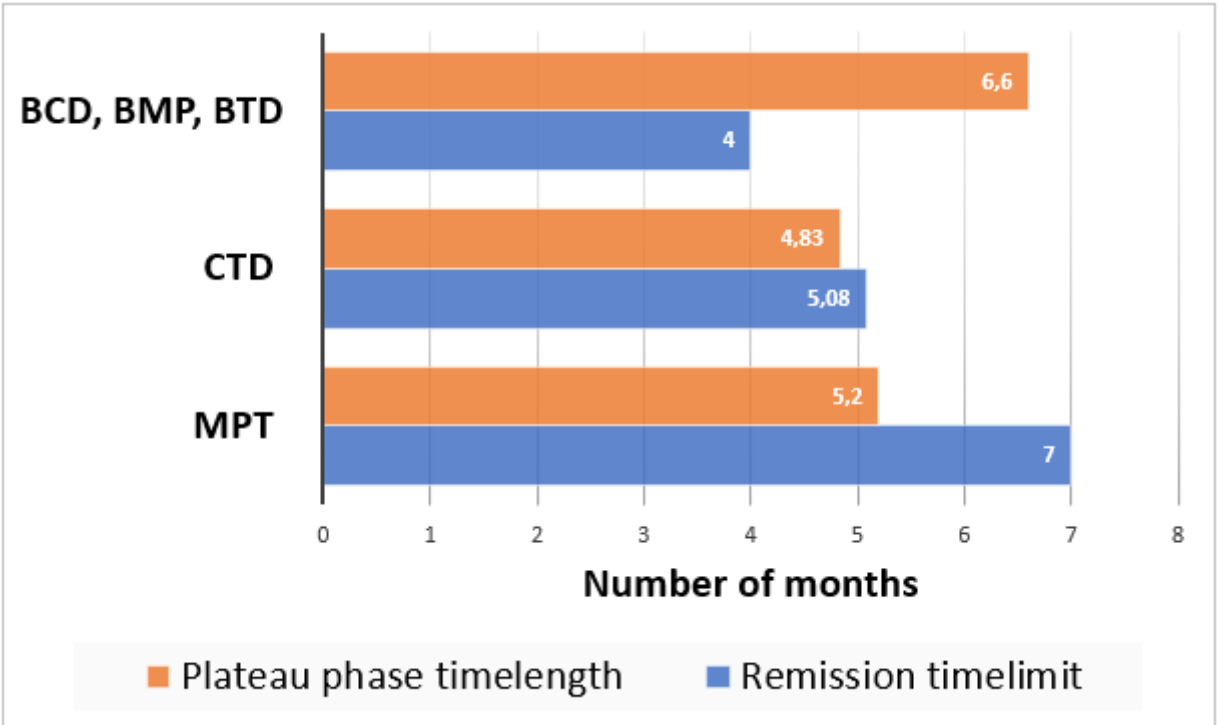


Figure 2: Time to remission and duration of plateau phase according to protocols

Discussion

There have been significant advances in the treatment of multiple myeloma in recent years, with an expansion of available drug therapies. The most recent therapies for multiple myeloma include the anti-CD38 monoclonal antibodies daratumumab and isatuximab, the exportin-1 inhibitor selinexor, the anti-B-cell maturation antigen (BCMA) conjugate antibody-drug belantamab mafodotin and the chimeric antigen receptor (CAR) T-cell therapy idecabtagene vicleucel [7]. The first-line treatment of younger patients is undoubtedly based on therapeutic intensification with autologous peripheral stem cell transplantation [14]. In Africa, and more precisely in Senegal, access to these new therapies is scarce; however, triple therapy gives fairly good results. Our study involved 36 patients who are followed at the clinical hematology department of the Dakar University Hospital. Triple therapy in multiple myeloma shows substantial results compared to the Alexanian protocol (MP) [8, 10]. The efficacy of bortezomib in multiple myeloma was a major breakthrough in the treatment of multiple myeloma [1]. In our study, protocols including bortezomib showed better results in both mean time to response and duration of progression-free follow-up. Similarly, studies have shown that myeloma patients receiving bortezomib benefited in terms of overall survival, progression-free survival and response rate compared to those who did not receive bortezomib [13]. However, they do not confer greater survival than the other protocols (MPT and CTD)[3]. Regarding the MPT and CTD protocols, few African studies have attempted to compare their results; in our study, the CTD protocol resulted in a faster remission than the MPT protocol. The duration of progression-free follow-up was approximately similar in patients on CTD and MPT. Nevertheless, survival was significantly better in patients who were on the TPM protocol. This could be due to the choice of the CTD protocol in patients with impaired renal function at diagnosis. Indeed, Mephalan, an anticancer drug that is imperatively recognized in the class of alkylating agents [9], is a nephrotoxic molecule that is more or less contraindicated in case of nephrological disturbances. On the basis of the current results, no definitive recommendation can be made regarding the comparative merit of the tested regimens. Nevertheless, and until the results of further studies are available, we recommend either CTD or MPT as appropriate first-line regimens for patients with multiple myeloma who are not candidates for transplantation in settings where lenalidomide and bortezomib are not available [8].

Conclusion

Thanks to recent therapeutic advances, the treatment of multiple myeloma is becoming increasingly promising. The results of our study show the efficacy of triple therapy in achieving a partial response as well as in the duration of progression-free survival. However, cases of non-response to triple therapy have been reported. Further studies would help to identify possible risk factors for non-response in order to adapt management at an early stage.

Authors' contributions

All authors have participated in the development of the article. The authors declare that they have read and approved the manuscript.

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