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REVIEW

Multiple Myeloma with Extramedullary Disease

Albert Oriol

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ABSTRACT

Plasmacytoma is a tumor mass consisting of atypical plasma cells. Incidence of plasmacytomas associated with multiple myeloma range from 7% to 17% at diagnosis and from 6% to 20% during the course of the disease. In both situations, occurrence of extramedullary disease has been consistently associated with a poorer prognosis of myeloma. Extramedullary relapse or progression occurs in a variety of clinical circumstances and settings, and therefore requires individualization of treatment. Alkylating agents, bortezomib, and immunomodulatory drugs, along with corticoids, have been used to treat extramedullary relapse but, because of the relatively low frequency or detection rate of extramedullary relapse, no efficacy data are available from controlled studies in this setting.

Keywords: extramedullary disease; multiple myeloma; plasmacytoma

Albert Oriol (✉)
Department of Hematology, Hospital Germans Trias i Pujol, Carretera de Canyet s/n. 08916 Badalona, Spain.
Email: aoriol@inconcologia.net

INTRODUCTION

Plasmacytoma is a tumor mass consisting of atypical plasma cells. When a single tumor is found and no evidence exists of systemic multiple myeloma (MM), it is classed as a solitary plasmacytoma. Epidemiologically, solitary plasmacytoma is 16 times less common than MM.[1] Although a significant proportion of solitary plasmacytomas subsequently progress to MM, it is not clear that plasmacytomas associated with MM, particularly those occurring during the course of disease, have the same pathogenesis as primarily localized disease. Incidence of plasmacytoma associated with MM at diagnosis ranges from 7% to 17%, depending on the studies.[2,3] The lack of precision and heterogeneity of these incidence and prevalence data clearly reflect the differences in approaches to diagnosis or comprehensiveness of imaging tests used for diagnostic and follow-up purposes at the different centers. Imprecision of data about the occurrence of extramedullary disease during the course of MM is even greater, with rates ranging from 6% to 20%.[2-4] The advent of more sensitive and easily available diagnostic tests (such as positron emission tomography [PET] and magnetic resonance imaging [MRI])

and prolongation of survival in MM patients are expected to increase the detection of extramedullary progression in the future.

Extramedullary progression of MM has consistently been associated with a poorer disease prognosis.[4,5] This poorer prognosis is not clearly related to the type or intensity of prior treatments and can not always be explained by occurrence of this progression in very advanced disease stages. There is increasing evidence that extramedullary relapse is associated with secondary changes in the myeloma clone, aggressive disease progression, poor prognostic histological and biological factors (plasmablastic morphology, higher proliferative index, and p53 expression), and treatment resistance.[6,7] It has also been reported that extramedullary progression or relapse is often associated with the "escape" phenomenon of the monoclonal component.[8]

It has been shown that the myeloma clone present in extramedullary plasmacytoma (EP) may have different characteristics as compared to the medullary clone responsible for systemic disease in the same patient.[9] Thus, in one patient[9] systemic disease responded to treatment used, while paraspinal disease was completely refractory. While certain primary genetic changes were present in both clones, p53 deletion was only detected in plasma cells taken from the paraspinal mass, but not in bone marrow cells.[9] These data support the hypothesis that extramedullary disease usually represents a tumor subclone that has acquired new secondary mutations, particularly p53 deletions, which would make it more resistant to treatment than the original medullary clone.

This article reviews the clinical and biological characteristics of MM when this is associated with the presence of EPs, and the role of radiotherapy and standard and new generation drugs (immunomodulatory drugs and proteasome inhibitors) in this setting based on the reported case series. A critical comparison is provided of data available on the different treatment options and, finally, a selection of clinical cases of practical management with lenalidomide of patients with MM and predominant extramedullary involvement are provided.

TREATMENT OF EXTRAMEDULLARY PROGRESSION IN MM

Most large pivotal trials in patients with relapsed MM have assessed the efficacy of study drugs in specific cytogenetic subtypes, particularly those considered to involve a poor prognosis, such as chromosome 17 deletions (del[17]), translocations involving the immunoglobulin heavy chain gene t(4;14) and t(14;16), chromosome 13 deletions (del[13]), or hypodiploidy.[10,11] However, specific efficacy in patients with plasmacytomas has not been differentially evaluated, partly because of the lack of specific and systematic diagnostic assessments of plasmacytomas in clinical trials. Phase 3 studies have not usually been designed with adequate power to define the role of conventional therapies or new drugs in specific cytogenetic subtypes. This specifically affects the relatively uncommon del(17), the change most consistently associated with extramedullary disease. Thus, in the absence of robust prospective data, our knowledge is based on analysis of a small series of cases.

Since the treatment of choice for solitary plasmacytoma is tumor irradiation, it is generally accepted that the best approach for a plasmacytoma associated with MM which requires specific control is radiotherapy. Radiotherapy and dexamethasone represent the standard emergency treatment for a paravertebral plasmacytoma causing medullary

compression. Based on current understanding of its particular biology, there is a high risk that the myeloma subclone of plasmacytoma is resistant to alkylating agents.[7] This would support the indication of radiotherapy together with the selected systemic treatment. There are also data suggesting a benefit of intensification treatment with high-dose melphalan in MM with extramedullary disease at diagnosis.[4] However, the most adequate induction treatment has not been defined, and the most effective rescue treatment when extramedullary disease occurs at relapse, particularly after treatment with high-dose melphalan, is not known either.

In a study where 42% of relapsing patients responded to thalidomide, 11 patients with extramedullary disease were studied.[12] While systemic response was achieved in most patients, extramedullary disease progressed in all of them. Despite the small sample size, this study provided a strong argument not to recommend thalidomide as the basis of treatment in extramedullary progression. However, isolated cases of plasmacytoma with good response to the combination of thalidomide and dexamethasone have been reported.[13] Other studies continue to support the use of thalidomide in this setting, but always combined with other drugs such as alkylating agents and corticosteroids.[14] In an ongoing trial of the Spanish Myeloma Group (GEM) where 18% of patients had EP, results of first-line treatment with bortezomib, thalidomide, and dexamethasone were significantly superior to those achieved with thalidomide and dexamethasone in patients with plasmacytomas at diagnosis.[15] The literature also supports the use of bortezomib for the treatment of extramedullary disease, but this recommendation is also based on the reporting of successful cases rather than on the study of a large series.[16-19]

Lenalidomide for the Treatment of MM and Extramedullary Disease

Clinical trials and large series reported with lenalidomide have the same limitations as studies of the above-mentioned drugs in terms of specific data about efficacy in plasmacytomas. The largest study of first-line lenalidomide treatment was reported by the Eastern Cooperative Oncology Group (ECOG).[20] This study did not report the proportion of patients who had extramedullary disease at diagnosis, or the proportion in whom extramedullary disease was the predominant form of progression. Other phase 2 studies assessing other lenalidomide combinations as first-line treatment have only been reported as abstracts, and may therefore not yet provide data about the efficacy of such combinations on extramedullary disease. The supposed benefit of intensification with high-dose melphalan in young patients after first-line treatment suggests that short induction therapy with lenalidomide and dexamethasone followed by autologous hematopoietic stem cell transplantation would be a valid approach for patients with predominant extramedullary disease and little systemic involvement. Unfortunately, none of the above studies provided data on this subject.

There are pivotal ongoing phase 3 studies intended to answer important questions regarding the use of lenalidomide in previously untreated patients not eligible for autologous stem cell transplantation (ASCT). The most relevant of such studies, MM020/FIRST trial is led by the Intergroupe Francophone du Myeloma (IFM). This study randomizes patients to receive 12 cycles of melphalan, prednisone, and thalidomide (MPT) for 18 months, 18 cycles of Rd (lenalidomide plus low-dose dexamethasone) for the same time period, or Rd until progression occurs. The trial should prove whether Rd is superior to the current standard MPT, and

will also compare the use of Rd for a given number of cycles to treatment until progression occurs. Follow-up of plasmacytomas present at diagnosis is mandatory in the trial, but there are no specific indications about the procedures to be used for identifying occult plasmacytomas during the initial work-up. Similar limitations are found in the relapsed and refractory setting. Over 700 patients were recruited into the pivotal MM009 and MM010 trials, which showed superiority of lenalidomide and dexamethasone over dexamethasone monotherapy,[10,11,21] but no data were reported in these studies for the subgroup of patients with extramedullary disease.

Lenalidomide is a drug that allows for achieving relatively rapid responses and could be the most adequate drug for patients with prior neuropathy, or even neuropathy induced by the plasmacytoma itself. It is therefore urgent to collect more information about the efficacy of the drug in patients with extramedullary involvement, and also in those with high-risk cytogenetic changes, particularly del(17p), the change most commonly associated with extramedullary progression. Since lenalidomide is effective in patients refractory to thalidomide,[22] a suboptimal effect of lenalidomide on extramedullary disease should not be assumed based on the doubts about the efficacy of thalidomide.

One of the best-studied series in this regard was recently published by Dr. J. M. Calvo-Villas et al.[23] This series collected retrospective data from 27 patients with disease progression or relapse together with the occurrence of an extramedullary mass. Median time from diagnosis of MM to occurrence of plasmacytoma was approximately 3 years, and median number of prior treatment lines received was three, including bortezomib in approximately 90% of cases. Some patients had also received high-dose melphalan and thalidomide. In 15 patients (55%), plasmacytoma represented extraosseous extension of a primarily bone lesion, while in the remaining 12 patients isolated masses occurred in noble and soft tissues. Multiple extramedullary disease was found in 10 patients (35%). The standard lenalidomide plus dexamethasone scheme was used in 70% of patients, while a third drug was added in the remaining patients. Median cycles received were 7 (range, 3-16), and additional radiotherapy on plasmacytoma was administered to eight patients only (30%). The overall response rate of plasmacytomas was 77% (46% of complete responses), and systemic disease responded in 70% of patients (31% with complete response). Rates were not significantly different in patients previously treated with bortezomib.

After a median follow-up of 1 year, median overall survival was 11 months. Fourteen patients were still alive (52%), of whom 10 continued on lenalidomide treatment, and subsequent progression or relapse was only recorded in four of the responding patients. Median progression-free survival was 9 months. Treatment-related toxicity was similar to that reported in prospective studies. Hematological toxicity was most common (grade 3-4 neutropenia in 33% of patients), but the number of infections was relatively low (11% of patients with febrile episodes). Deep vein thrombosis occurred in two patients. The study therefore suggested a significant efficacy of lenalidomide in this indication. In the absence of literature data based on large retrospective studies, documentation of additional cases and small series provides information especially relevant for daily practice in the management of extramedullary progression or relapse.

In the above examples, the use of lenalidomide in specific clinical situations allowed for

control of myeloma with predominant extramedullary disease.

CONCLUSION

Incidence of plasmacytoma associated with MM at diagnosis ranges from 7% to 17% depending on studies, while the occurrence rate of extramedullary disease during the course of myeloma ranges from 6% to 20%. Extramedullary progression of MM has consistently been associated with a poor disease prognosis. There is increasing evidence that extramedullary relapse is associated with secondary changes in the myeloma clone, aggressive disease progression, poor prognostic histological and biological factors, and treatment resistance.

The most significant clinical trials of the main drugs used for the treatment of myeloma have not specifically assessed the efficacy of treatment in patients with plasmacytomas. Overall, phase 3 studies have not been designed with an adequate power for defining the role of new drugs in the patient subgroup with extramedullary involvement, and our knowledge is based on analysis of a small series of case reports.

It is recognized that radiotherapy added to the systemic treatment of choice is the best approach to a plasmacytoma associated with MM that requires specific control. Data about the preferred systemic treatment are scarce and are not based on direct comparisons. There is only adequate evidence that thalidomide would not be one of the most adequate drugs in this situation. In a GEM group trial, results of first-line treatment with bortezomib, thalidomide, and dexamethasone were significantly superior to those achieved with thalidomide and dexamethasone in patients with plasmacytomas at diagnosis.

Recent data suggest that lenalidomide could be an effective and manageable drug for patients with MM-associated EP, as the drug may achieve relatively rapid responses. It is therefore urgent to collect more information about the efficacy of the drug in patients with extramedullary disease, and also in those with high-risk cytogenetic changes, particularly del(17p), the change most commonly associated with extramedullary progression.

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