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Secondary Monoclonal Gammopathy of Undetermined Significance Is Frequently Associated with High Response Rate and Superior Survival in Patients with Plasma Cell Dyscrasias

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A B S T R A C T

Secondary monoclonal gammopathy of undetermined significance (MGUS) is a special phenomenon that occurs during the treatment of multiple myeloma (MM). The incidence, biological characteristics, and prognostic value of secondary MGUS in patients with MM remain undefined. We proceed with a retrospective systematic review of serum immunofixation electrophoresis studies performed in 438 cases of patients with plasma cell dyscrasias, including 409 cases of newly diagnosed MM and 29 cases of primary plasma cell leukemia. Secondary MGUS was more common in patients with myeloma who had undergone stem cell transplantation than in those who had not (17 [29.8%] of 57 versus 5 [1.4%] of 352, $P < .001$). The clinical parameters and cytogenetic characteristics in patients with or without secondary MGUS were comparable. The complete response rates in patients with or without secondary MGUS were 81.8% and 21.8% respectively ($P < .01$). For the cohort as a whole, secondary MGUS was associated with significantly prolonged progression-free survival (median, 52.0 months versus 22.5 months; $P = .002$) and overall survival (median, not reached versus 35.0 months; $P < .001$). The presence of secondary MGUS retained independent prognostic value with a moderate impact on overall survival (hazard ratio .128 [95% confidence interval .018 to .922]; $P = .041$) in the multivariate Cox regression model. However, when analysis was restricted to patients undergoing stem cell transplantation, no statistical differences in progression-free survival and overall survival were found. In conclusion, we observe that secondary MGUS was frequently observed in MM patients after transplantation and conferred a survival prolongation. The favorable survival in patients with secondary MGUS may be explained by beneficial effect from myeloablative therapy.

INTRODUCTION

Single serum monoclonal protein of constant isotype and light-chain restriction are hallmarks of multiple myeloma (MM). Practically, both serum and urine M-protein concentrations are used to stage myeloma patients and to document responses to treatments [1]. Occasionally, some patients may develop new monoclonal gammopathies of an isotype (heavy and/or light chain) distinct from the original M component after treatment, which are termed secondary monoclonal gammopathy of undetermined significance (MGUS) [2,3]. The pathophysiology of secondary MGUS is not clear, and the incidence and clinical features of secondary MGUS in patients with MM remain undefined.

The prognostic value of secondary MGUS is still an open question. Most studies showed that the appearance of secondary MGUS was associated with prolonged survival [2,4], whereas other studies show contradicting results [3]. Moreover, it is still unknown whether the beneficial effect of secondary MGUS is from high depth of response or low-risk underlying genetic features.

To address this issue, we explored the prevalence, clinical characteristics, and prognostic significance of secondary MGUS in a cohort of newly diagnosed MM and primary plasma cell leukemia (pPCL) patients. Our study demonstrated that secondary MGUS had a beneficial impact on survival in the overall series; however, it lost prognostic value when analysis was restricted to patients undergoing stem cell transplantation (SCT). No clinicobiological characteristics related to a favorable prognosis were found in patients with secondary MGUS. The superior outcome may be explained by beneficial effect from myeloablative therapy.

MATERIALS AND METHODS

Patients

We identified 438 cases of patients with plasma cell dyscrasias between January 2004 and December 2012, with a median follow-up of 3 years. These

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patients included 409 newly diagnosed with MM and 29 with pPCL. Patients were classified as MM and plasma cell leukemia (PCL) according to the International Myeloma Working Group [5].

According to their request, patients were assigned to either the thalidomide-based or bortezomib-based treatment. Thalidomide-based treatment consisted of 4 cycles of induction treatment with (thalidomide 200 mg/day, adriamycin 9 mg/m^2 administered intravenously on days 1 to 4, and dexamethasone 20 mg/day orally or intravenously on days 1 to 4 and 9 to 12; or thalidomide 200 mg/day, cyclophosphamide 300 mg/m^2 intravenously on days 1 and 8, and dexamethasone 20 mg/day orally or intravenously on days 1 to 4 and 9 to 12); bortezomib-based treatment consisted of 4 cycles of induction treatment with BCD (bortezomib 1.3 mg/m^2 intravenously on days 1, 4, 8, and 11; cyclophosphamide 300 mg/m^2 intravenously on days 1 and 8; and dexamethasone 20 mg/day, orally or intravenously, on days 1, 2, 4, 5, 8, 9, 11, and 12) or PAD (bortezomib 1.3 mg/m^2 intravenously on days 1, 4, 8, and 11; adriamycin 9 mg/m^2 intravenously on days 1 to 4; and dexamethasone 20 mg/day orally or intravenously on days 1, 2, 4, 5, 8, 9, 11, and 12). After at least 4 cycles of treatment with partial remission or better, patients underwent consolidation therapy, which was either autologous stem cell transplantation (ASCT) or chemotherapy with the patient's original regimen according to their request. Subsequently, patients were treated with thalidomide (100 mg/day to 150 mg/day) for 1 year to maintain the response. When necessary, some of them also received supportive treatment with zoledronic acid every 1 to 2 months and erythropoietin or granulocyte colony-stimulating factor. All patients underwent prophylactic acyclovir treatment.

Identification of Patients with Secondary MGUS

Patients who developed a secondary MGUS were identified through a retrospective analysis of serum immunofixation electrophoresis (IFE). IFE test was performed with Sebia Hydragel kits on the Sebia Hydrasys electrophoresis system (Sebia, Norcross, GA) using agarose gels. The identification of secondary MGUS required the detection of at least 1 new monoclonal (M) protein with heavy and/or light chain immunoglobulin different from the initially diagnosed MM [2].

Fluorescence in Situ Hybridization

All MM samples were purified using the Miltenyi technology (Miltenyi Biotec, Paris, France) with anti-CD138–coated magnetic beads before fluorescence in situ hybridization (FISH) analysis as previously reported [6]. Plasma cells were then analyzed using DNA probes specific for the following chromosomal aberrations: del(13q14), del(17p), t(11;14), t(4;14), and t(14;16). Gains of 1q21 were assessed using a bacterial artificial chromosome probe at 1q21 (RP11-307C12) [7]. A total of 200 interphase nuclei were analyzed. The cut-off values recommended by the European Myeloma Network were used: for deletions and numerical aberrations, the cut-off level was set at 20%; for translocations in the IgH locus, as well as other translocations, the cut-off level was set at 10% [8].

Serum-free Light Chain Measurements

The serum-free light chain (FLC) concentrations were measured nephelometrically using Freelite automated immunoassay (Binding Site, Birmingham, United Kingdom) on an IMMAGE II system (Beckman Coulter, Krefeld, Germany). Our previous study has determined the reference range of serum free κ and λ light chains in a group of Chinese patients. For the κ to λ free light chain ratio (rFLC), the 95% reference interval was .27 to 1.35 [9].

Statistical Analyses

The primary end point was the correlation with survival from the time of diagnosis. Progression-free survival (PFS) was calculated from the initiation of therapy to the date of death, progression, or last follow-up. Overall survival (OS) was measured from the initiation of treatment to the date of death or last follow-up, according to the International Uniform Response Criteria [10]. Two-sided Fisher exact tests were used to assess associations between categorical variables, with a confidence coefficient of 95%. Survival curves were plotted using the Kaplan-Meier method, with differences assessed with the log-rank test. Results were considered significant if the P value was less than or equal to .05.

RESULTS

Prevalence of Secondary MGUS in Patients with Plasma Cell Dyscrasias

Two hundred and forty patients with untreated, symptomatic MM were treated with thalidomide-based therapy, among whom 11 patients underwent ASCT. One hundred and fifty-nine myeloma patients received bortezomib-based therapy and 44 of them received ASCT. Eight patients were treated with lenalidomide and 2 patients were treated with allogeneic bone marrow transplantation. In the PCL patients, 3 were treated with high dose therapy (HDT)/ASCT, 2 with allogeneic bone marrow transplantation, 20 with thalidomide-based therapy, and 4 with bortezomib-based therapy.

A total of 26 of the 438 patients (5.9%) developed secondary MGUS. No statistical difference was found between MM and PCL patients (22 [5.4%] of 409 for MM versus 4 [13.8%] of 29 for PCL, respectively; $P = .06$). Secondary MGUS was much more common in patients with myeloma who had undergone SCT than in those who had not (17 [29.8%] of 57 patients versus 5 [1.4%] of 352, respectively; $P < .001$).

In myeloma patients receiving bortezomib- or lenalidomide-based chemotherapy, secondary MGUS was observed in 10.9% (18 of 174) of the patients versus 1.7% (4 of 235) of those receiving thalidomide-based chemotherapy ($P < .001$). In the cases of ASCT, secondary MGUS was observed in 27.3% (3 of 11) of patients with MM receiving thalidomide-containing regimens as induction therapy versus 30.5% (14 of 46) of those receiving bortezomib-based therapy before transplantation. No statistical difference was found between these 2 groups ($P = .29$). In patients who were ineligible for high-dose therapy and transplantation, secondary MGUS was detected in 2.4% (3 of 123) of cases receiving bortezomib- or lenalidomide-based therapy versus .9% (2 of 229) of those receiving thalidomide-based chemotherapy. The difference between these 2 groups was not significant either ($P = .31$).

Characteristics of Secondary MGUS

The main characteristics of myeloma patients who developed secondary MGUS are shown in Table 1. All patients with secondary MGUS produced only 1 new monoclonal protein. The most common oligoclonal immunoglobulin was IgG κ (69.2%), followed by IgG λ (15.4%), free κ (7.7%), IgM λ (3.8%), and IgA λ (3.8%). The median time from diagnosis to secondary MGUS occurrence was 9.2 months (95% confidence interval [CI], 2.0 to 34.8 months). Among SCT patients, the median time from the date of ASCT to the development of secondary MGUS was 4.4 months (95% CI, .3 to 19.1 months). Secondary MGUS was detected at more than 12 months after ASCT in 9 cases (56.2%), while at less than 12 months after ASCT in 7 cases (43.8%). The median duration of secondary MGUS from appearance to disappearance was 4.4 months (range, .3 to 19.1 months).

Clinical and Biological Significance of Secondary MGUS

As shown in Table 2, there was no significant difference between MM patients with or without secondary MGUS in either the median age or distributions determined by the International Staging System stage, Durie-Salmon stage, immunologic subtypes, and patterns of antigen expression.

As the genetic changes have emerged as the most important prognostic factors in myeloma patients, we examined chromosome aberrations by FISH. According to the Intergroupe Francophone du Myelome stratification of the myeloma model, high-risk MM was defined as the presence of any 1 or more of the following criteria: deletion of 17p13, or t(4;14), or t(14;16) [6].The distribution of chromosomal aberrations was similar in both groups. It seemed that the occurrence of secondary MGUS was associated with a lower frequency of del(13q), and high-risk chromosome aberrations were uncommon. However, these differences were not statistically significant.