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Perspectives and Commentaries

Serum Beta 2 Microglobulin in Multiple Myeloma. A Critical Review

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THE SURVIVAL of patients with multiple myeloma (MM) is quite variable, ranging from a few weeks to several years. Thus, in individual patients and in any large randomized study to prevent very disparate results, it is very important to have careful pretreatment evaluation of prognostic factors. Many prognostic factors have documented importance in MM [1], but the most important and widely used indicators are (a) extent of bone-marrow involvement by myeloma cells and tumor mass; (b) renal status and (c) several intrinsic properties of tumor cells, including immunoglobulin type and light chain subtype, chromosome ploidy, nucleic acid content, histological and proliferative characteristics and intrinsic drug sensitivity [2–14]. Unfortunately, some of these parameters are difficult or inconvenient to evaluate serially in individual patients or routinely in some medical centers and therefore cannot be widely applied. In order to simplify the prognostic evaluation of patients with MM, several myeloma staging systems (MSS) have been proposed, generally based on the combination of those variables found to be the most predictive of survival duration. These MSS include the Durie–Salmon (DS) MSS [3], the Medical Research Council (MRC) MSS [15] and the Merlini–Waldenstrom–Jayakar (MWJ) MSS [16]. More recently, several histological gradings were proposed [6, 9, 13]. In spite of their well-proven validity, these methods present some problems, particularly with regard to their inter-reproducibility which can fail with some borderline patients. This difficulty is in part attributable to the problems of assessing the extent of lytic bone lesions in the DS-MSS, as well in evaluating the percentage of myeloma cells in the bone marrow in the MWJ-MSS and quantifying the degree of symptoms (i.e. performance status) in the MRC-MSS. The number of misclassified patients can be important in large multicenter studies. In addition, while these methods are valuable in the initial prognosis, they do not allow for an evaluation of response to chemotherapy, quality of remission, plateau-phase and kinetics and disease progression in individual patients. In this context, the interest of serum beta 2 microglobulin (SB2M) in the clinical evaluation and management of patients with MM deserves some comment. The main characteristics of this small molecule (B2M) and its importance in clinical immunology have recently been reviewed [17, 18].

SERUM BETA 2 MICROGLOBULIN IS A POTENT DISCRIMINATIVE MARKER OF PROGNOSIS AT DIAGNOSIS IN MM

High SB2M levels in MM were reported as early as 1973 [19] and the secretion of free B2M by human myeloma cell lines as early as 1974 [20]. During the last 10 years, several studies have shown that B2M, although a non-specific cell molecule, could behave as a reliable 'tumor marker' of lymphoproliferative disorders, especially MM [1]. To date, *fourteen prospective studies* following that

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of Norfolk (1979) [22] have demonstrated that SB2M levels in MM influence survival duration, patients with the highest levels having the shortest survival [10, 22–34]. Some cut-off levels (4 μg/ml for Norfolk [22], 6 μg/ml in our experience [25]) appeared to maximize the exclusion of patients with a good prognosis (i.e. SB2M levels < cut-off values: long survival) from the higher SB2M group. Of major interest, several studies have shown that the prognostic value of SB2M remained strong in myeloma patients without renal failure or with a similar tumor mass (i.e. high myeloma cell mass for example) [22, 26]. Therefore, it was thought that SB2M levels reflected not just tumor burden and/or renal status which are of major prognostic value (and with which there is a direct correlation) but probably disease activity or intrinsic drug sensitivity and kinetics. In eight recent studies, the prognostic value of SB2M was directly compared (often by multiple regression analyses) to that of the main presenting features of patients, of the three available MSS (i.e. DS-, MRC- and MWJ-MSS) and of some intrinsic properties of tumor cells, including RNA and DNA content and kinetics (i.e. labeling index) [10, 23, 25, 29–33]. With two exceptions [32, 33], it was exciting to see that the prognostic value of SB2M alone was as or more powerful than that of the major prognostic parameters previously used in MM. When SB2M was simply combined with either hemoglobin [29] or serum albumin [31], the prognostic information given by this combination was superior to that of any available MSS. Of major interest was the observation that DNA content [10] or labeling index [30] of tumor cells did not add major information to that given by SB2M alone. *In terms of survival, therefore,* from the currently available data, it is easy to conclude that SB2M is a powerful marker for pretreatment staging and stratification of MM. Furthermore, the use of SB2M alone or in association with either hemoglobin or serum albumin as suggested recently [29, 31] has the very great advantage of permitting classification at diagnosis based upon simple reproducible serum methods and follow-up. *Although SB2M levels do not predict response to chemotherapy* [10], the percentage of myeloma patients with primary treatment failure and disease progression is significantly higher in patients with high SB2M levels (i.e. levels > 6 mg/l) [10]. In our experience, in the case of patients treated by at least three courses of chemotherapy, a progression was observed in 54% of the high SB2M levels group of patients as opposed to 24% of the opposite group ($P < 0.02$). This is another argument for postulating that the prognostic value of SB2M was not simply related to tumor burden and/or renal status [35]. Further investigations on both the biology of B2M and of myeloma are necessary to clarify this special point. Studies to evaluate correlations with labeling index, DNA and RNA content, *in vitro* drug sensitivity and some other biologic parameters are therefore worthwhile. Studies performed on fresh tumor samples suggest that free B2M is spontaneously released in human myeloma bonemarrow and that the major part of this B2M comes from tumor cells, especially in the case of very active disease [36, 37]. However one of our concerns comes from the observation of a lack of B2M production *in vitro* and *in vivo* in a small subset of patients with MM, especially some IgA and low or non-secretory cases (but not IgG cases) [26, 27, 38]. This could be a limit for the use of B2M as a marker of disease activity in these patients [38]. Further investigation of this special subgroup of patients will be necessary. Recent and interesting findings have suggested that the lack of B2M shedding observed in some patients with MM could be related to unusual Gm allotypes [39].

SERUM BETA 2 MICROGLOBULIN IS RELATED TO DISEASE ACTIVITY

SB2M levels remain of prognostic value during the course of the disease [10, 26–29] and several studies are now available to clearly demonstrate that serial measurements of SB2M levels are of interest in the subsequent monitoring of patients with MM having abnormal SB2M levels at the time of diagnosis [10, 22, 23, 26–29, 35]. The successful completion of a plateau-phase is associated with a significant reduction of SB2M levels, patients achieving the best remission (i.e. 2 logs tumor mass regression) having the lowest SB2M levels in plateau [26]. Patients with less than 2 mg/l SB2M in plateau were found to belong to a subset of very good prognosis, regardless of the severity of presenting clinical features [26]. On the other hand, more information is needed about the prognostic value of SB2M in relapse. We and others have previously reported that very high SB2M levels were observed in fulminant relapses, with fast growing tumors and/or renal deficiency [26, 27]. However, a more careful evaluation of disease progression in 90 personal patients with MM (comparing several 'markers' of progression), revealed a lack of B2M to predict progression in 9% of the cases, before the occurrence of renal deficiency, especially in IgA and low or non secretory MM [26, 38], these patients retaining normal SB2M levels. Of major interest is the fact that the monoclonal protein was often deficient in the same subset of patients to inform on disease progression and that new cytic bone lesions and/or hypercalcemia were (in many of these cases) the early clues of disease activity [38].

CONCLUSIONS

From the previously cited data and although some special points have to be clarified, it is already clear that SB2M measurement can give the clinician valuable help in MM. As recently emphasized by the MRC, SB2M appears to be 'a key measurement for assessing the prognosis and response to treatment of patients with MM' [29]. The best use of B2M as a prognostic indicator could be the initial staging of patients in large randomized studies to prevent disparate results. Indeed, using SB2M *alone* or in combination with hemoglobin in the MRC-MSS and/or serum albumin according to our own data, a simple stratification of patients can be proposed, for comparison of the initial groups of patients [29, 31]. Since SB2M clearly appears to be more powerful than serum creatinine in predicting survival, *a simpler alternative proposal could be to substitute B2M for creatinine in the DS-MSS.* Prospective studies in which patients would be randomized or treated on the basis of their initial SB2M values would be useful to clarify this point of view. On the other hand, SB2M does not appear to be useful to the diagnosis of MM. Indeed, SB2M can not clearly distinguish a monoclonal gammopathy of undetermined significance (MGUS) from an early MM in an individual patient. Although the SB2M levels tend to be lower in MGUS than in low cell mass MM, there is overlap between the two groups [26, 27]. During remission induction, SB2M levels correlate with disease activity and SB2M in plateau gives a reliable information on the importance of tumor regression in patients with high SB2M levels at diagnosis. This could be the best information given by SB2M. This indicates that SB2M measurements could be helpful at diagnosis (for a comparative staging) and in plateau (for assessment of individual response to treatment). However, the clinician has to keep in mind that, like for the monoclonal protein, some MM retain normal SB2M levels during all the follow-up.

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