

Proteomic analysis of serum for identification of potential biomarkers predicting response of patients with refractory multiple myeloma to bortezomib-based therapy

Ota Fuchs

Institute of Hematology and Blood Transfusion, Prague, Czech Republic

Plasma cell myeloma, or multiple myeloma (MM), is a clinically heterogeneous, incurable hematological malignancy of end-stage B lineage cells. It accounts for approximately 1% to 2% of newly diagnosed cases of cancer worldwide.¹ The availability of novel therapies for the treatment of MM has a dramatic impact on the depth of response to triplet therapies, particularly in relapsed or refractory patients.^{2,3} The addition of proteasome inhibitors such as carfilzomib and ixazomib or the monoclonal antibodies such as the anti-CS1 (also known as signaling lymphocytic activation molecule family member 7 [SLAMF7]), monoclonal antibody elotuzumab, or anti-CD38 monoclonal antibody daratumumab to a treatment combination of lenalidomide and dexamethasone has been reported. Fewer results have been obtained with triplet therapies based on a combination of bortezomib and dexamethasone. The addition of the histone deacetylase inhibitor panobinostat or rolinostat or the monoclonal antibodies elotuzumab or daratumumab has also been studied.^{2,3}

The study of Łuczak et al⁴ in this issue of *Polish Archives of Internal Medicine (Pol Arch Intern Med)* is very important for identification of drug-resistance biomarkers as the first step to individualization of treatment for refractory MM. Human serum is easily collected by a noninvasive procedure and does not require expensive preparation to analyze. The preliminary study of the same authors was presented at the American Society of Hematology meeting in December 2016.⁵ This research group has recently proved that proteomics can be successfully used to describe proteins that differentiate the bone marrow plasma cells with complete or very good partial response (CR/VGPR) to bortezomib-based

therapy from those patients who are refractory to this treatment.⁶⁻⁸

Bone marrow plasma cells are obtained by an invasive method of bone marrow biopsy, which is not useful in routine clinical practice. Therefore, Łuczak et al⁴ have used proteomic analysis of serum to overcome this obstacle. They used nano-liquid chromatography–tandem mass spectrometry to analyze digested serum protein samples from 61 proteasome inhibitor-naive, transplant-eligible patients with MM, who were resistant to the first-line chemotherapy protocol CTD (cyclophosphamide, thalidomide, and dexamethasone) and were scheduled for salvage PAD (bortezomib, adriamycin [doxorubicin], and dexamethasone) or VTD (bortezomib, thalidomide, and dexamethasone) chemotherapy. This analysis is an efficient method for identification of differentially expressed proteins in serum from patients with MM.

Based on their response to therapy according to the International Myeloma Working Group criteria,⁹ Łuczak et al⁴ classified patients with MM into 3 groups: CR/VGPR (24 patients), partial response (PR; 19 patients), and stable or progressive disease (SD/PD; 18 patients). A comparative proteomic analysis between these groups was performed. A total of 16 upregulated and 35 downregulated proteins were identified in the sera of patients derived from the PD/SD group compared with the CR/VGPR group. The most highly correlated differential protein was thyroxine-binding globulin (TBG), which increased proportionally to response to bortezomib-based therapy. A severe acquired decrease in TBG levels was previously described in a patient with MM.¹⁰ The human TBG gene was identified on chromosome Xq22.2 by fluorescence in situ hybridization. Little

Correspondence to:

Ota Fuchs, PhD, Institute of Hematology and Blood Transfusion, U nemocnice 1, 12820, Prague 2, Czech Republic, phone: +420 221 977 313, e-mail: ota.fuchs@uhkt.cz

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information is available about the biosynthesis and turnover of TBG. It is synthesized primarily in the liver as a 54-kDa protein.

Apolipoprotein C-1 was also positively correlated with the depth of response to bortezomib-based therapy. On the other hand, quiescin sulfhydryl oxidase 1 (QSOX1) was found to be upregulated in the SP/PD group in comparison with the CR/VGP group. Protein stability, assembly, localization, and regulation depend on the formation of disulphide bonds between cysteine side chains. QSOX1 is an enzyme that oxidizes thiols during protein folding, reducing molecular oxygen to hydrogen peroxide. Tumor cells may take advantage of oxidative environments at different stages of tumor progression.¹¹ However, there is some controversy as to whether QSOX1 is a marker of poor or favorable outcome in breast cancer.¹¹ It may also have additional functions in tumors.

Complement components were found to be downregulated (C7 and C4) or upregulated (C9) in the PD/SD group in comparison with the CR/VGP group. The proteomic analysis in relation to C-reactive protein (CRP) showed the upregulation of this protein in the SP/PD group in comparison with the CR/VGP group. Validation studies of CRP levels were conducted using an enzyme-linked immunosorbent assay to confirm the results of the proteomic analysis. The results obtained by both methods were found to be in agreement. CRP is a common marker of inflammation. CRP promoted proliferation of MM cells and protected MM cells from chemotherapy-induced apoptosis.¹² CRP activates PI3K/Akt, ERK, and NF- κ B signaling pathways.¹²

Identification of biomarkers allows the prediction of therapy outcome with specific agents and may help avoid resistance. Further studies are needed to analyze and validate the role of proteins from the obtained proteomic signature.

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