Sudden Significant Total Protein Concentration Change: Not an Analytical Problem

Goce Dimeski^{1*} and Peter Wood²

¹*Department of Chemical Pathology, Pathology Queensland, Princess Alexandra Hospital,
Woolloongabba, Queensland, Australia*

²*Department of Haematology, Pathology Queensland, Princess Alexandra Hospital,
Woolloongabba, Queensland, Australia*

Sudden and significant total protein concentration changes in multiple myeloma (MM) can be associated with new treatment regimens. We present an example of a 66-year-old male with a total protein concentration of 74 g/L, albumin 27 g/L, and a monoclonal IgG concentration of 22.2 g/L before commencing lenalidomide treatment. The patient represented 8 days later and the total protein concentration was 66 g/L, albumin 32 g/L with a monoclonal IgG concentration of 10.3 g/L. The total protein and albumin measurements were performed on Beckman DxC800 analysers using bieuiret and bromocresol purple methods, respectively (Beckman Coulter Diagnostics, Fullerton, CA). The IgG was performed on Beckman Image analyser (Beckman Coulter Diagnostics). It is regularly observed that patients with the new drug treatments have total proteins, more accurately the specific immunoglobulin decreasing significantly in a matter of days. Generally, the remaining biochemical profiles undergo minimal change. To laboratorians such a major significant change in total protein concentration will trigger alarms (including possibly delta check flags) of possible analytical errors: sampling accuracy or possible assay interference. This leads to additional investigations by laboratorians, which would include sample integrity checks (sufficient volume, microclots, bubbles), possible re-analysis, running additional quality control samples, changing total protein reagents, withholding of results until communication with other professionals including the clinical unit occur, and leading to delay in reporting of the results and added costs.

MM is currently an incurable hematological malignancy. Monoclonal gammopathy, a common predisposing disease, occurs in ~3% of persons 50 years of age or older (1). It is characterized by the clonal expansion of monoclonal immunoglobulin-secreting plasma cells within the bone marrow. The overall median survival for patients with MM without treatment is

approximately 3 years. It is the second most common hematologic malignancy, and the most common cancer to involve bone. The cause of MM is unclear. Exposure to radiation, herbicides, insecticides, benzene, and other organic solvents may play a role.

Until recently the standard treatment involved a combination of oral melphalan and prednisolone. Allogeneic transplantation was first attempted in the early 1980s, and it became routine therapeutic practice in the 1990s (2), but is not widely used due to high treatment-related mortality. Autologous stem cell transplant (ASCT) has become the treatment of choice. For patients unable to undergo ASCT, including elderly patients (>65 years), or patients relapsing after ASCT there have been few treatment options. Singhal et al. in 1999 (3) indicated that thalidomide, an oral agent with anti-angiogenic and immunomodulatory properties, was able to induce objective responses in 30% of patients with refractory and advanced MM. In 2006, thalidomide was approved by the US FDA, and more recently lenalidomide (approved by FDA in 2006, European Union in June 2007), a thalidomide analog with up to 50,000-fold increased potency, (4) and bortezomib, a proteasome inhibitor (approved by US FDA in May 2003), have been added and used as salvage agents for the treatment of relapsed and refractory MM. Trials of these agents as frontline therapy are underway with very promising initial results. These new drugs are cytotoxic to MM cells in the bone marrow. Therefore, rapid and significant changes in total protein concentrations, globulin or specific immunoglobulin are expected.

*Correspondence to: Goce Dimeski, Department of Chemical Pathology, Pathology Queensland, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Queensland 4102, Australia. E-mail: gdi56790@bigpond.net.au; goce_dimeski@health.qld.gov.au

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TABLE 1. Examples of Patients With Major Changes in Total Protein and Globulin in Days as Result of Multiple Myeloma Treatment With the New Drugs

Patient	Drug	Total protein change (g/L)	Albumin change (g/L)	Globulin change (g/L)
A	Bortezomib	−42 in 10 days	−4 in 10 days	−38 in 10 days
B	Lenalidomide	−28 in 13 days	0 in 13 days	−28 in 13 days
C	Thalidomide	−15 in 7 days	−1 in 7 days	−16 in 7 days

Examples of such major decreases are presented in Table 1. In our observation, such rapid drops are almost always (~70–80% of patients) when these new drugs are used as first line treatment. Whereas decrease in globulin concentrations are less pronounced when these drugs are used as secondary treatments, and in fact a much smaller percentage (~30%) of patients respond and actually show globulin decrease.

Review of the literature clearly indicates there is excitement about the level of effectiveness of these new drugs in increasing complete remission rates and remission durations with MM. It also indicates long-term survival after treatment with stem-cell transplantation or the newly developed drugs is rare, and disease recurs in virtually all patients (5). But the literature does not provide an indication of the possible extent of the change expected in total protein concentration with these new drug treatments to put at ease routine laboratorians when encountering such sudden and significant changes. The case presented here clearly demonstrates the rapid biochemical changes that may occur with these agents and which were very uncommon with prior therapies. Paraprotein reductions with melphalan and prednisolone therapy do not occur with this rapidity and are usually 5–10 g/L/month. More

rapid changes in paraprotein (and hence globulin and total protein level) may be seen after ASCT but such patients are usually easily identified by other biochemical and hematologic changes and probably clinically notified. These rapid and unexpected biochemical changes will become a more common observation with the increasing use of novel therapies such as thalidomide, thalidomide analogs (lenalidomide), and proteasome inhibitors (bortezomib) both as single agents and in the future in combination.

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