Editorial

Central Nervous System Myeloma and New Drugs: Can we Begin the Fight?

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Since the introduction of novel agents (thalidomide, lenalidomide, bortezomib) into clinical practice, the median overall survival (OS) from the time of diagnosis for transplant-eligible patients with multiple myeloma (MM) improved greatly from 3–4 years to 7–8 years [1-3]. On the other hand extramedullary localization of MM to central nervous system (CNS-MM) still has a dismal prognosis. CNS-MM, i.e. leptomeningeal involvement, is rare and accounts for about 1% of the patients with MM. Primary parenchymal brain lesions without osseous or dural contact without leptomeningeal involvement are even rarer [4]. Given the lack of clinical series and the peculiar localization within a "sanctuary", the management of IC-MM is a clinical challenge. This may result from the nature of the blood-brain barrier (BBB) which constitutes a natural protection from several drugs that are commonly utilized for the treatment of MM. Other three barriers are present at interfaces of blood vessels, i.e. the blood-arachnoid barrier, the blood-retinal barrier, and the blood-nerve barrier. There are diverse treatments for CNS-MM, which include systemic chemotherapy (CHT), intrathecal therapy, (IT), and radiotherapy (RT), with median survivals between 1 and 6 months. Recent discoveries on the fundamental molecular mechanisms behind MM cell growth and survival have led to the introduction of novel classes of pharmacologic agents such as the immunomodulatory drugs (IMiDs) and proteasome inhibitors (bortezomib). However, the activity of new drugs against IC-MM is largely unknown. Although bortezomib does not cross the BBB, and thalidomide and lenalidomide are reported by their activity against intracranial tumors other than MM has been described recently, probably because of the manufacturer to have only a minimal crossover, disruption of the BBB and increased vascular permeability within the tumor [5,25]. In fact in one study clinical and biological data were retrospectively reported regarding patients presenting with an osteo-dural or primary dural multiple myeloma (OD/D-MM) or a central nervous system myelomatosis (CNS-MM). New therapies were used in 35/50 patients whereas 15/50 patients received old chemotherapy treatments. Twenty-five out of 50 patients obtained a complete remission or a very good partial remission (CR+VGPR). Median OS for CNS-MM was 6 months, for OD/D-MM 25 months. OS for IC-MM patients treated with new agents was 25 months vs. 8 months for patients treated with old agents. Improved OS and PFS were predicted by: response (CR+VGPR),by patients who received SCT vs. CHT. Stem cell transplants (SCT) plus novel agents and RT seemed the better choice for younger eligible patients. SCT has been reported in the past as a treatment capable of prolonging survival, even in the era of old agents, signifying that dose intensification could be important also in this set of patients [10]. Second generation IMID's and proteasome inhibitors hold promise to be more effective and to ameloriate responses in CNS-MM. Pomalidomide (CC-4047) – a novel immunomodulatory derivative (IMID) with a stronger *in vitro* anti-myeloma effect compared with "older" IMIDs – thalidomide and lenalidomide [24]. It may induce apoptosis via caspase-8, inhibit angiogenesis and cytokine secretion, and impede the interactions between stroma and myeloma cells. Moreover, it down-regulates tumor necrosis factor-α. Pomalidomide has shown encouraging results with a single case series demonstrating efficacy against extramedullary MM [26] and a recent case report illustrating its efficacy in CNS MM [6]. Pre-clinical studies in rats have shown

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pomalidomide penetrates the BBB, highlighting its potential for therapy against CNS disease (unpublished observations).

Marizomib, is a natural β-lactone compound obtained from the marine bacterium *Salinospora tropica*. This unique class of PI is non-peptidic; its β-lactone ring can irreversibly inhibit proteasomal activities *in vitro* and *in vivo*. NPI-0052 exhibited a prolonged pan-proteasome inhibitory effect in an animal model, with more than 70 % inhibition of all three protease activities after twice weekly dosing and rapid distribution to tumor tissue after administration. The apoptotic cascade activation by NPI-0052 is more dependent on extrinsic (caspase-8-mediated) apoptotic signaling, in contrast to bortezomib, which is dependent on both extrinsic and intrinsic (caspase-9) apoptotic pathways. This agent also has oral bioavailability. A phase I study of marizomib in relapsed/refractory MM revealed CNS toxicity with dysphasia and ataxia, suggesting entry through the BBB and therefore a potential therapeutic agent in CNS MM [28].

These new molecules that can have some effects in CNS-MM need to be tested in to prospective large clinical trials, set to recruit enough number of patients. In particular the International Myeloma Working Group (IMWG) should be active investigating biology, genetics and new strategies also in this rare form of myeloma. The fight to CNS myeloma can begin!

CONFLICT OF INTERESTS STATEMENT

Authors declare no conflict.

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