Phase I Study of Atacicept in relapsed/refractory multiple myeloma (MM) and Waldenström's macroglobulinemia (WM).

Jean-François Rossi MD PhD

Department of Haematology, University Hospital and INSERM U847, Montpellier-France

B-lymphocyte stimulator (BLys, CD257, also know as B-cell-activating factor (BAFF) and A proliferation-inducing ligand (APRIL, CD256) support B-lymphocyte maturation and stimulate the growth of malignant plasma cells. BLys and APRIL share 2 receptors, transmembrane activator and CAML interactor (TACI, CD267) and B-cell maturation antigen (BCMA, CD269). BLys also binds to a third receptor, BAFF-R, CD268). In addition to the aberrant expression of one of these receptors by myeloma cells, bone marrow environment was shown to produce large amounts of BLys and APRIL, mainly by myeloid cells, monocytes and osteoclasts. In WM, APRIL and BLys have been also described as potent survival factors for tumoral cells.

Atacicept (from SeronoMerck Inc.) is a fusion protein composed of the human IgGFc portion and the extracellular, ligand-binding protein of the TACI receptor, which neutralises both BLys and APRIL. Atacicept was demonstrated as effective for blocking the proliferation of myeloma cells and inducing their apoptosis *in vitro*. The results of this open-label phase-I study was partly published in BJC 2009, 101:1051-58. This study was conducted in our department and started in november 2004. Sixteen patients with advanced disease (12 MM and 4 WM) received one cycle of five once-weekly injections of atacicept by subcutaneous route (2, 4 and 7 mg/kg). Patients with stable disease after cycle I were included in an extension study (either 2 additional cycles (2, 4 and 7 mg/kg cohorts or 15 consecutive weekly injections of atacicept at 10 mg/kg). Atacicept was well tolerated including at the injection site. The maximum tolerated dose was not identified. Of 11 patients with MM who completed initial treatment, 5 patients were progression-free after cycle 1 and 4 patients were progression-free after extended therapy. Of 4 patients with WM, 3 patients were progression-free afeter cycle 1. At the end of the extension study, 2 patients were progression-free with a minimal response for 1 patient and the other had stable disease. No progression of the tumour mass was observed in the 2 patients who had lymph node involvement at the study entry. Consistent with atacicept mechanism of action, polyclonal immunoglobulin isotypes and total B cells were reduced. Bone marrow density, myeloma cells and numbers and plasma concentrations of soluble CD 138 also decreased. The biological effect of atacicept was more pronounced in patients with WM. Atacicept did not affected the inflammatory biomarkers. Of the 16 patients tested at baseline, 13 had measurable levels of free APRIL ($\geq$25 ng/ml). In contrast, only 3 patients had baseline free BLys concentrations above the limit of quantification (1 .6ng/ml). In this small number of patients, no correlations were apparent between baseline levels of free APRIL and biological or clinical response criteria. Atacicept is well tolerated in patients with MM and WM, with clinical and biological activity linked to its mechanism of action.