FILLING THE GAPS: PEG-INTERFERON IN THE UNDER-TREATED WORLD OF SYSTEMIC MASTOCYTOSIS

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Unlike advanced forms of Systemic Mastocytosis (SM) - which may respond to tyrosine kinase inhibitors such as midostaurin or avapritinib - indolent and smoldering subtypes (ISM and SSM) typically lack indications for cytoreductive treatment. Their management remains largely symptomatic, focusing on mediator blockade with antihistamines leukotriene inhibitors, and mast cell stabilizers. The absence of disease-modifying therapies in non-advanced SM highlights an unmet need, particularly for patients with debilitating symptoms or complications such as osteoporosis and fractures, where current options offer limited disease control. While traditionally recognized for its antiviral and immunomodulatory properties, peg-interferon-alfa2a (peg-IFN-α) has been reported to show an effective role in osteoporosis associated with mast cell disorders. In a cohort of 12 patients currently under follow-up at Azienda Ospedaliera Universitaria Pisana (F:M= 1.2, median age of 54 years old) diagnosed with ISM or SMM (according to WHO 2022) and presenting with osteoporosis, treatment with low-dose peg-IFN-α (90–135 µg subcutaneously per week) was started in association with bisphosphonates over a median follow-up of 59 months. All patients had experienced at least one prior fragility fracture or presented with osteolytic lesions at baseline. The medium tryptase level at diagnosis was 63.8 mcg/L. Following initiation of peg-IFN-α, no new fractures were documented in 11 patients. The evaluation through Bone Mineral Densitometry (BMD) revealed a stabilization of the osteolytic lesions in 5 patients and a regression of the osteoporosis pattern in 3 patients (median Z-score at diagnosis -3.6 vs median Z-score after 24 months -3.1). Bone turnover markers, including serum alkaline phosphatase, showed significant reductions, suggesting decreased osteoclastic activity. Moreover, patients reported reduced bone pain and improved physical function. Only one patient showed progression of disease and was started on cytoreductive treatment. While adverse effects such as mild flu-like symptoms and fatigue were reported in a subset of patients, treatment was generally well tolerated. Only one patient presented cardiac arrhythmias, which brought to the suspension of the treatment in order to perform surgical atrial correction. Another patient discontinued the treatment for recurrent fungal respiratory infection. The medium tryptase level at 24 months was 28.6 mcg/L (Figure 1-2). These preliminary findings support the potential of peg-IFN-α as a disease-modifying strategy to prevent progression of bone damage in selected patients with ISM and SSM who exhibit refractory or high-risk bone involvement. Unlike osteoporosis, where it appears to reduce osteoclastic activity, its impact on osteoblastic hyperactivity or sclerotic bone lesions has not been systematically studied. These outcomes suggest that peg-IFN-α may play a protective role in halting skeletal deterioration in non-advanced SM, likely by reducing mast cell burden and suppressing the release of bone-resorptive mediators