

Treatment of myelodysplastic syndrome with agents interfering with inhibitory cytokines

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Pathogenetic mechanism

The clonal myeloid haemopathies, including myelodysplastic syndromes (MDS), comprise a group of disorders whose phenotypic expression relates to abnormal haemopoietic regulation. Targets of this dysregulation include cellular programmes for stem cell survival, proliferation, differentiation, and inhibition. The dysregulation occurring in MDS is related to both abnormalities within the patients' haemopoietic stem cells and in their marrow stromal support mechanisms.^{1 2}

The stem cell abnormalities in MDS include altered levels of apoptosis (programmed cell death), immune dysregulation, telomere shortening, and enhanced oxidative stress susceptibility. The marrow stromal derangements in this disorder, which enhance apoptosis, include increased paracrine production of inhibitory cytokines (for example, tumour necrosis factor α (TNF α), transforming growth factor β , Fas ligand) and suboptimal production of stimulatory cytokines (G-CSF, GM-CSF, interleukin 3, erythropoietin), which together diminish the survival and differentiation of these haemopoietic stem cells.^{3–11} Such paracrine anomalies enhance intracellular activation of apoptosis-generating proteases (caspases), which underlie much of the pathogenesis of this disorder.¹²

Studies have shown that increased apoptosis contributes to the ineffective haemopoiesis and peripheral cytopenias present at early stages of MDS.^{4–6} Conversely, excessive survival/decreased apoptosis of progressing abnormal clonal cells occurs upon evolution of MDS into acute myeloid leukaemia. These intracellular apoptotic related phenomena are associated with switches within the haemopoietic precursors from an increased ratio of pro-apoptotic:anti-apoptotic oncoprotein expression into a reversal of this ratio.^{4–6}

Therapeutic trials

Experimental therapeutic approaches are being aimed at blocking many of these lesions. To attempt to diminish the inhibitory effects of TNF α and its associated cytopenias in MDS, patients were treated with TNF receptor-fusion protein (TNFR-FP, Enbrel).¹³ The protocol was based on in vivo and in vitro data: Studies in patients with rheumatoid arthritis showed clinical benefit and improvement in their associated anaemias when treated with TNFR-FP.^{14 15} In vitro investigations with MDS marrow showed that TNFR-FP resulted in significantly increased haemopoietic colony formation.¹⁵ In this phase I/II trial 14 patients with various subtypes of MDS were treated.¹³ TNFR-FP 25 mg was given twice weekly subcutaneously for eight weeks, followed by either

continued treatment at the same dose for responders or at three doses/week for another eight weeks for non-responders. All patients had previously received red blood cell or platelet transfusions, or both, and one or multiple other treatment modalities.

Overall, treatment was well tolerated, though four patients developed antibiotic responsive infections (two requiring admission to hospital and in whom TNFR-FP was discontinued prematurely). Of the remaining 12 patients, five were responders: four had erythroid responses with improvements in haemoglobin of 1–1.5 g/l or a 50% decrease in transfusion requirement; two of these patients also showed 54% and 73% increases in platelet counts. Two patients (one additional to the erythroid responders) showed 63% and 120% increments in neutrophils. Except for an increase in marrow blasts from 15% to 25% in one patient, marrow blasts remained stable after treatment, and marrow cytogenetics did not change. Before treatment, marrow plasma TNF α levels were raised relative to controls in all patients, but did not correlate with in vivo responses.

Thalidomide, a drug which has multiple effects, including diminishing TNF α production and which is anti-angiogenic and immunomodulatory, has also been used to treat MDS. In a pilot trial 33 patients were treated, of whom 20 were evaluable for response.¹⁶ Preliminary information indicates haematological improvement in 10 of these patients, treated with 100–400 mg/day for several months. Side effects, known to be substantial with this agent, were not reported. Clinical investigations are continuing, expanding the experience with this drug.

Summary

Results of these trials provide evidence for biological activity and some clinical efficacy of agents potentially blocking inhibitory cytokines in patients with MDS. However, given the limited responses, it appears that factors additional to TNF α inhibitory activity contribute to the development of cytopenias in these patients. Further studies are warranted using anti-TNF α /anti-inhibitory cytokine approaches, either alone or in combination with other agents, capable of abrogating the effects of additional inhibitory mechanisms in MDS.

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