Trial Watch

GIST NATURAL KILLERS

Although *KIT* mutational status is predictive of response to the KIT inhibitor imatinib (Glivec; Novartis) in patients with gastrointestinal stromal tumours (GISTs), some patients who were predicted to be non-responders have responded to imatinib, possibly because the drug also promotes the production of interferon-γ (IFNγ) by natural killer (NK) cells, which is immunostimulatory. In a retrospective analysis of patients with GISTs, Guido Kroemer, Laurence Zitvogel and colleagues have observed differential expression of splice variants of the NK cell receptor NKp30, which affects NKp30 function and patient prognosis.

Analysis of 44 GIST samples from patients at diagnosis showed tumour infiltration by NK cells, but NK cell abundance did not correlate with the Miettinen prognostic score and was not changed by imatinib therapy. However, NKp30 was downregulated in tumour-infiltrating NK cells.

The functions of three NKp30 isoforms (produced by alternative splicing of the *NCR3* gene) were characterized in a human NK cell line. Cells expressing either the NKp30a or the NKp30b isoform, but not the NKp30c isoform, produced IFNγ following receptor engagement. When co-cultured with tumour cells, NK cells expressing NKp30a produced large amounts of IFNγ and blocked tumour cell growth. NKp30b cells produced a small amount of IFNγ, whereas NKp30c cells produced the immunosuppressive cytokine interleukin-10 (IL-10).

Quantitative reverse transcription PCR (RT-PCR) on peripheral blood mononuclear cells (PBMCs) from 80 patients with GISTs revealed that in 44, either NKp30a or NKp30b was the most abundant isoform (profile AB), whereas 36 expressed predominantly NKp30c (profile C); this was stable over time regardless of treatment or disease progression. In addition, various lines of evidence indicated defective NK effector functions in purified NK cells from profile C patients, which could be overcome by blocking IL-10.

To analyse the effect of NKp30 isoform expression on overall survival, a retrospective analysis of 80 patients with GISTs who had been treated with imatinib was conducted (mean follow-up 58 months, range 12–103 months). Profile C patients had a reduced overall survival (median 79 months) compared with profile AB patients (median not reached, $P = 0.001$). Furthermore, profile AB patients were more likely to survive following progression on imatinib (five deaths from 20 relapses versus 15 deaths from 21 relapses in profile C patients, $P = 0.006$).

Single nucleotide polymorphisms (SNPs) in *NCR3* were identified that reduced the transcription of NKp30a and NKp30b, causing preferential expression of NKp30c. Although carrying these SNPs was not as predictive of survival as being profile C, profile C patients who also carried these SNPs were found to have a dismal prognosis.

Beyond the potential of NKp30 as a biomarker, further understanding of the role of NK cells and NKp30 isoforms in GISTs could lead to new immunotherapy options for this disease.

ORIGINAL RESEARCH PAPER Delahaye, N. F. *et al.* Alternatively spliced NKp30 isoforms affect the prognosis of gastrointestinal stromal tumors. *Nature Med.* 8 May 2011 (doi:10.1038/nm.2366)