

Preview

Autologous cellular therapy for myeloma: Giving *ex vivo* expanded NK cells their due

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Ex vivo feeder-free autologous NK cell expansion is an efficient modality for clinical translation. In this issue of *Cell Reports Medicine*, Nahi et al. describe the use of this approach as consolidation therapy for multiple myeloma,¹ thereby reviving an alternate avenue for NK cell therapy.

Multiple myeloma remains an incurable disease. Autologous stem cell transplantation (ASCT) remains one of the mainstays of available intensive therapies for eligible patients, often followed by long-term maintenance therapy with either an immunomodulator or proteasome inhibitor.² However, with a median age of diagnosis of 65–70, intensive therapies that attain remission and maintain long-term control of disease may be challenging to administer.³ Furthermore, the long-term use of maintenance therapy has a number of important side effects, including a higher risk of cytopenia, thrombotic events, secondary malignancy with lenalidomide, and neuropathy with proteasome inhibitors.⁴ The use of an alternative cellular therapy as consolidation following ASCT is an interesting and promising approach without these potential side effects.

In this era of immunotherapy, NK cell therapies are coming into their own. With recent developments in the ability to purify, expand, and manipulate NK cells both *ex vivo* and *in vivo*, a new armamentarium of cellular therapy to complement T cell therapies is being developed for clinical application. Various methods have been developed for the generation and *ex vivo* expansion of NK cells for clinical use, including the use of feeder layers expressing membrane-bound IL-15 or IL-21 in addition to costimulatory molecules such as 4-1BB, as well as feeder-free approaches.⁵ Nahi et al. demonstrate an adaptation of the latter approach, showing the feasibility of generating a clinical grade product for infusion in an efficient and cost-effective manner¹. Such an approach, with the added advantage of using a closed system that re-

duces the risk of product contamination, is amenable to scale.

While most NK cell therapies are allogeneic in origin, with their clinical efficacy in part dependent on HLA mismatch between donor and recipient,⁶ autologous NK cell therapy is nevertheless a viable consolidative strategy. Autologous products are easier to procure and do not suffer from some of the challenges of HLA mismatched cellular therapy; namely, failure to persist in an immune incompatible milieu and the off-target activation of the cellular product due to an abundance of targets in a non-immune compatible allogeneic recipient leading to exhaustion or anergy.⁷ The latter excessive off-target activation that can result in NK cell exhaustion or anergy is prevented when the predominant target remains the tumor.

Expansion and long-term persistence of adoptively transferred immunologically autologous NK cells has also been demonstrated in trials of cytokine-induced memory-like (CIML) NK cells collected from an allogeneic donor and infused into an immune compatible post-allogeneic stem cell transplant environment.^{8–10} Although technically derived from an allogeneic donor, these CIML NK cells were in fact autologous to the hematopoietic system of the recipient who previously received an allogeneic stem cell transplant from the same donor. The immune compatible environment facilitated the expansion and persistence of the post-transplant NK cell compartment. Furthermore, these cytokine-activated NK cells exhibited augmented activity against tumor targets and were associated with clinical responses when treating myeloid disease.^{8–10}

As with other trials of autologous or immune compatible NK cell therapy, the adoptive transfer of *ex vivo* expanded NK cells is well-tolerated.^{1,9} With a number of available platforms supporting the expansion and persistence of adoptively transferred NK cells, further enhancement of their cytotoxic potential with the use of chimeric antigens is a logical next step and an exciting way forward.¹⁰ As with leukemia and myelodysplastic syndrome where early phase NK cell therapy clinical trials have demonstrated feasibility and efficacy, multiple myeloma may represent the expansion of the myeloid frontier in which NK cell therapy is given its due.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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