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Commentary

Cell Therapy for Solid Tumours: From an Exceptional iNKT-Cell Response to a Testable Therapeutic Platform

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The case report by Cheng et al., published in the Journal of Clinical Question, describes an exceptional clinical course in which an HIV-positive patient with recurrent EGFR L858R-mutated lung adenocarcinoma achieved complete remission lasting more than 6 years after treatment with allogeneic invariant natural killer T (iNKT) cells combined with dendritic cells (DCs).[1] The patient remained free from documented disease progression after four treatment cycles and treatment discontinuation, with only grade 1–2 adverse events reported. Although a single case cannot establish causality or define therapeutic efficacy, this prolonged remission represents a clinically important observation. It invites careful consideration not only of iNKT-cell therapy itself but also of the broader potential of cellular immunotherapy in solid tumours. Because both iNKT cells and DCs were administered, the outcome cannot be attributed specifically to either component. The case is therefore interpreted here as hypothesis-generating evidence for an allogeneic iNKT-cell and DC combination strategy rather than as definitive evidence of iNKT-cell monotherapy.

The significance of this case should be considered within the evolving field of cellular immunotherapy for solid tumours. Major platforms include tumour-infiltrating lymphocytes (TILs), T-cell receptor (TCR)-engineered T cells, chimeric antigen receptor T cells, natural killer-cell platforms and invariant or stem cell-derived products.[2] These approaches differ in antigen dependence, manufacturing complexity, persistence and toxicity. Their relevance lies primarily in clarifying the distinctive biological and translational rationale for iNKT-cell-based therapy rather than in providing a comprehensive review of every platform.

The significance of this case should be interpreted within the rapidly evolving field of cell therapy. Cellular immunotherapy for solid tumours now includes tumour-infiltrating lymphocytes, genetically engineered T-cell receptor T cells, chimeric antigen receptor T cells, natural killer and CAR-NK cells, γδ T cells, iNKT cells, dendritic-cell vaccines and allogeneic or induced pluripotent stem cell-derived platforms. These approaches differ in antigen recognition, manufacturing complexity, persistence, toxicity and dependence on the tumour microenvironment. Nevertheless, they share a common therapeutic objective: to generate durable antitumour immunity in cancers that remain difficult to control with conventional systemic therapy. However, TIL and neoantigen-specific TCR approaches remain

peptide- and HLA-dependent and generally require individualized manufacturing.[3] In tumours with low mutational burden, limited neoantigen availability or HLA downregulation, CD1d-restricted glycolipid recognition by iNKT cells may offer a complementary, rather than directly competing, strategy.[4]

These conditions can also impair iNKT cells: repeated TCR stimulation may induce anergy, while hypoxia, inhibitory cytokines and metabolic stress may restrict their function. Their translational rationale therefore lies not in proven intrinsic resistance to exhaustion, but in rapid effector activity, reduced dependence on classical HLA and the capacity to coordinate NK cells, DCs and conventional T cells.[5]

Human iNKT cells use a semi-invariant TCR to recognize glycolipid antigens presented by the monomorphic CD1d molecule. This pathway may bypass classical HLA loss, although direct tumour recognition still requires adequate CD1d expression and lipid-antigen loading. Activated iNKT cells can promote DC maturation through CD40L-dependent signals and IFN-γ/IL-12 crosstalk; licensed DCs may then cross-prime host CD8+ T cells and broaden antitumour immunity.[4,6] Because Cheng et al. administered both cell types, such reciprocal activation is biologically plausible, but the contribution of each component remains unknown. The phase I study of allogeneic iPSC-derived iNKT-cell monotherapy supports platform feasibility, but it does not establish efficacy comparable to the durable response observed with the combination. Comparative clinical cohorts are therefore required.[7]

The EGFR L858R genotype adds another unresolved variable. A direct relationship between EGFR L858R and tumour CD1d expression or lipid-antigen presentation has not been established. Oncogenic EGFR signalling can suppress CXCL9, CXCL10 and CXCL11 expression in lung adenocarcinoma, potentially limiting CXCR3-dependent recruitment of effector lymphocytes.[8] Future studies should assess tumour CD1d expression, lipid-antigen processing, chemokine gradients and intratumoral iNKT-cell localization before and after treatment.

Autologous cellular therapies are often constrained by prolonged patient-specific manufacturing, high cost, variability in starting-cell fitness and impaired lymphocyte function after previous anticancer treatment. Healthy-donor, induced pluripotent stem cell and hematopoietic stem and progenitor cell platforms may instead enable standardized, scalable, off-the-shelf products.[9] The phase I study of allogeneic iPSC-derived iNKT cells in recurrent head and neck cancer demonstrated a manageable safety profile and preliminary biological activity, while Li et al. reported a clinically guided method for generating allogeneic CAR-NKT cells from hematopoietic stem and progenitor cells.[7,9] Translation nevertheless requires reproducible lineage differentiation and expansion, elimination of residual undifferentiated cells, genomic stability, preservation of the invariant TCR and an NKT1-like phenotype, consistent post-thaw potency and avoidance of prolonged stimulation that may promote anergy or terminal differentiation. Manufacturing and engineering strategies may seek a Th1-biased product with strong IFN-γ cytotoxic activity and limited IL-4 or IL-13 secretion, but excessive polarization could increase inflammatory toxicity and requires prospective safety assessment.[5]

Safety terminology should distinguish graft-versus-host disease (GVHD), in which donor immune cells attack recipient tissues, from host-versus-graft rejection, in which recipient immunity eliminates the infused cells. Because iNKT cells recognize CD1d through an invariant TCR, they are expected to carry a lower risk of graft-versus-host disease than conventional allogeneic αβ T cells. However, residual risk may remain if the product contains contaminating conventional T cells or undergoes genetic modification, particularly HLA-disrupting engineering intended to prolong cell persistence.[10] Host-versus-graft rejection may be more relevant to persistence and repeat dosing.[11] During repetitive allogeneic infusions, serial monitoring could include donor-cell chimerism or product-specific polymerase chain reaction, donor-specific anti-HLA and panel-reactive antibodies, recipient T- and NK-cell activation and circulating IFN-γ, IL-6, TNF, IL-2, IL-4, IL-10, CXCL9 and CXCL10, together with routine inflammatory and organ-function parameters.

Recent clinical progress has provided important proof of principle. In a randomized phase III trial, Rohaan et al. demonstrated that tumour-infiltrating lymphocyte therapy improved progression-free survival compared with ipilimumab in patients with advanced melanoma.[12] The subsequent accelerated approval of lifileucel for unresectable or metastatic melanoma further established cellular therapy as a clinically validated strategy for selected solid tumours.[13] Similarly, Leidner et al. reported

neoantigen-specific T-cell receptor gene therapy targeting KRAS G12D in metastatic pancreatic cancer, showing substantial regression of visceral metastases in a patient with a typically treatment-refractory malignancy.[14] Together, these studies indicate that cellular therapy for solid tumours is no longer only conceptual, but is gradually entering a phase of clinical translation.

Despite these advances, the application of cell therapy to solid tumours remains challenging. Unlike hematologic malignancies, solid tumours are characterized by heterogeneous antigen expression, impaired antigen presentation, dense stromal architecture, abnormal vasculature, hypoxia, nutrient deprivation and an immunosuppressive microenvironment. Regulatory T cells, myeloid-derived suppressor cells, tumour-associated macrophages, inhibitory cytokines and checkpoint pathways may all restrict cellular trafficking, persistence, expansion and cytotoxic function.[15] Therefore, effective cellular therapy in solid tumours requires more than infusion of tumour-reactive cells; it requires sustained tumour access and preservation of effector function within a hostile immune contexture.

The allogeneic nature of the therapy is also clinically relevant. Autologous cellular therapies are often limited by manufacturing time, cost, patient-specific variability and treatment-related lymphocyte dysfunction. In contrast, allogeneic products derived from healthy donors or induced pluripotent stem cells may offer a more standardized and scalable "off-the-shelf" approach. A recent phase I study of allogeneic induced pluripotent stem cell-derived iNKT cells in recurrent head and neck cancer showed a manageable safety profile and preliminary biological activity.[7] These findings support the feasibility of iNKT cells as a broader therapeutic platform. At the same time, allogeneic therapy requires careful evaluation of persistence, host-versus-graft rejection, alloimmunization, cytokine-mediated toxicity and long-term safety.

The patient's HIV-positive status further increases the translational interest of this case. People living with HIV have historically been underrepresented in immunotherapy and cell-therapy trials, despite improved viral suppression and immune restoration with modern antiretroviral therapy. HIV infection may influence T-cell differentiation, immune exhaustion, cytokine biology, infection risk and antitumour immune competence. Therefore, successful administration of cell therapy in this context is noteworthy, but future reports should include detailed information on viral load, CD4+ and CD8+ T-cell counts, antiretroviral treatment, opportunistic infection history and longitudinal immune profiling. Such data are essential to determine whether similar approaches can be safely extended to immunologically complex populations.

Accordingly, the apparent tolerability of iNKT-cell and DC combination therapy is noteworthy but should not be generalized from a single patient. Direct effects of specific antiretroviral therapy (ART) classes on the persistence, proliferation or cytotoxic signalling of infused allogeneic cells are not established. Effective viral suppression may be favourable, whereas older nucleoside reverse-transcriptase inhibitors can impair mitochondrial function and pharmacologically boosted regimens may create drug–drug interactions; these remain theoretical concerns rather than demonstrated effects on iNKT-cell products.[16] Future reports should therefore document the exact ART regimen, HIV viral load, CD4+ and CD8+ T-cell counts, organ function, opportunistic infection history, concomitant medications, cytokine profiles and infused-cell kinetics.

Taken together, this case is a clinically important but hypothesis-generating observation. Prospective evaluation should validate the signal in larger cohorts, separate the contributions of iNKT cells and DCs, define tumour CD1d and immune biomarkers, and assess donor-cell persistence, host rejection, alloimmunization, GVHD, cytokine-mediated toxicity, durability and reproducibility. Such studies will determine whether allogeneic iNKT-cell-based combination therapy can become a testable and scalable platform for solid tumours, including immunologically complex populations.

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Hisashi Nagai conceived the commentary, critically reviewed and interpreted the relevant literature, drafted and revised the manuscript, approved the final version and accepts full responsibility for the accuracy and integrity of the work.

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Generative AI Declaration

Generative AI was not used.

Ethical Statement

Not applicable.

Conflict of Interest

The authors report no conflicts of interest in this work.

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