Neurological Complications Across Immunotherapies

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THIS INSIGHTFUL educational session, titled 'Neurologic complications across immunotherapies – a comparative perspective', was held at the 52nd Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT). It explored neurologic complications associated with modern haematologic therapies, including allogeneic haematopoietic cell transplantation (allo-HCT), CAR-T cells, and other immunotherapies. While these treatments have improved outcomes, they introduce complex neurotoxicities affecting patient care. Featuring Petra Hühnchen, Charité - Universitätsmedizin Berlin, Germany; Charlotte Graham, King's College London, UK; Roser Velasco, Catalan Institute of Oncology-University Hospital of Bellvitge, Barcelona, Spain; and Dionysios Neofytos, Division of Infectious Diseases, University Hospital of Geneva, Switzerland, and chaired by Ana Alarcón, Hospital Puerta de Hierro, Madrid, Spain; and Olaf Penack, Charité – Universitätsmedizin Berlin, Germany, the session provided a comprehensive overview of risk factors, mechanisms, and management strategies.

NEUROLOGICAL COMPLICATIONS OF ALLOGENEIC HCT

Hühnchen opened the session by speaking on neurological complications of allo-HCT. She stressed the disparity in reported frequencies of neurological complications of allo-HCTs, highlighting several factors that can affect reporting in the literature, such as study design, patient population, duration of follow-up, and definitions of complications.[1-3] She noted that over 50% of adult allo-HCT patients experience neurologic symptoms, approximately 20% have probable or proven diagnoses, and approximately 6–15% develop central nervous system (CNS) complications.

Elaborating on CNS complications, Hühnchen highlighted the wide range of neurological complications that patients can experience. These include cerebrovascular and neuromuscular graft-versus-host disease (GvHD), cognitive and neuropsychiatric encephalopathy, neurological complications of medical procedures, and therapy-related neurotoxicities, amongst others. Referencing a 2024 study, she noted that overall survival is typically lower in patients who experience a CNS complication compared to those who do not.[4]

Hühnchen posed two questions to the audience. First, what are the risk factors for neurological complications? Risk factors include older age, reflecting increased vulnerability of the ageing brain to complications, as well as total body irradiation, acute GvHD, chronic GvHD, and tacrolimus.[4] Additionally, all types of acute leukaemia, specifically acute lymphoblastic leukaemia and acute myeloid leukaemia, are considered significant risk factors for neurological complications due to infiltration of leukaemic cells into the CNS, as well as associated metabolic disturbances and increased susceptibility to infections.

Second, what are the causes of neurological complications? Approximately 25–35% are considered infectious, 45–57% non-infectious, and 18–24% are unclassified. The most common causes of infection are viruses (35%), followed by fungal (29%), toxoplasmic (27%), and bacterial (9%).[5]

After outlining the risk factors and causes, Hühnchen discussed the expected timeline of CNS infections following allo-HCT.[6,7]

The three major stages include haematopoietic stem cell transplantation (HSCT) conditioning, which is a preparatory regimen of high-dose chemotherapy, immunotherapy, or radiation given before a haematopoietic stem cell transplant; HSCT engraftment, in which transplanted haematopoietic stem cells travel to the patient's bone marrow and begin producing new, healthy blood cells; and immunosuppression, which is stopped to allow the donor cells to adapt to the recipient's immune system. Typically, the quantity of CNS infections is highest nearer the beginning of the process than the end; however, the specific types vary. For instance, around Day 0 (HSCT conditioning), a conditioning regimen and supportive care toxicities, as well as metabolic complications, are most common, whilst at Day 30, bacterial, antibiotic, human herpesvirus 6 (HHV-6), and fungal infections predominate. Finally, around the Day 180-mark, opportunistic infections, Herpesviridae reactivation, and GvHD are common, but still have a relatively low incidence.

Hühnchen noted that there are several challenges in detecting CNS infections in allo-HCT: these patients are severely immunocompromised, and infections can be caused by rare or opportunistic pathogens, making it harder to identify the cause. Additionally, clinical presentation is often atypical, and there is a low pathogen burden in cerebrospinal fluid (CSF). However, several novel diagnostic tools, such as metagenomic next-generation sequencing, have shown recent potential in detecting CNS infections in allo-HCT patients.

Finally, Hühnchen spoke on non-infectious neurologic complications, which most commonly occur within the first year following transplant, with approximately 30% occurring due to drug-induced neurotoxicity. However, as stressed by Hühnchen, defining the root cause can be challenging, as there is a multifactorial genesis to non-infectious CNS complications, with vascular, infectious, metabolic, and immune-mediated factors all playing a role.

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In summary, Hühnchen's talk highlighted the heterogeneous and multifactorial nature of neurological complications following allo-HCT, with wide variability in reported incidence and clear implications for survival. She emphasised key risk factors such as age, GvHD, and conditioning intensity, and outlined the diverse aetiologies, where non-infectious causes predominate, but infections remain significant and difficult to diagnose. Overall, she underscored the complexity of these complications and the need for improved diagnostic approaches in this immunocompromised population.

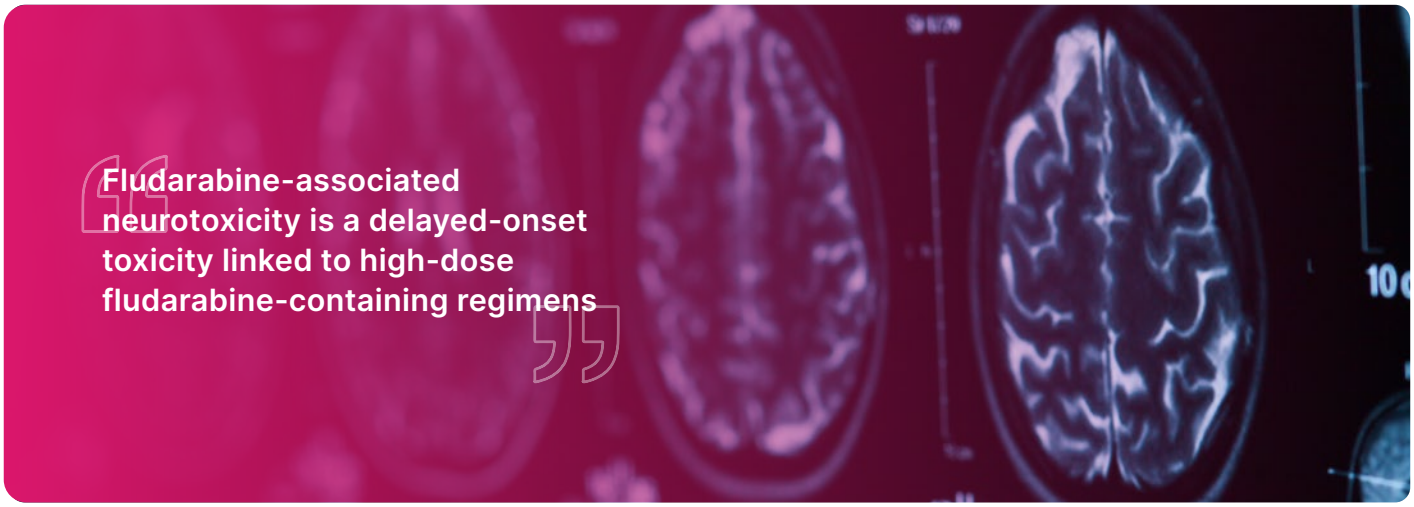
NEUROLOGICAL COMPLICATIONS OF CAR-T THERAPY

Graham then addressed the specific neurological complications associated with CAR-T therapy. CAR-T cells are engineered cells that become activated upon binding to tumour cells. Once activated, an inflammatory signalling cascade is triggered. Graham then spoke on immune effector cell-associated neurotoxicity syndrome (ICANS), which is commonly seen with cluster of differentiation (CD)19 and B cell maturation antigen (BCMA) CAR-T cells. Patients with ICANS may experience encephalopathy, dysphasia, somnolence, myoclonus, and seizures.

Interestingly, there are currently ongoing clinical trials that aim to address the associated toxicity with CAR-T cell therapy, namely the early use of siltuximab, an IL-6 binding monoclonal antibody targeting cytokine release syndrome (CRS) and ICANS.[8] Additionally, early or prophylactic use of anakinra may reduce the incidence of severe ICANS.[9,10]

However, ICANS and CRS are not the only complications associated with CAR-T cell therapy. As noted by Graham, other neurological complications include movement and neurocognitive toxicity, cranial nerve palsy, ischaemic stroke, myelitis, peripheral neuropathy, Guillain-Barré syndrome, tumour inflammation-associated neurotoxicity, and fludarabine-associated neuropathy.

Movement and neurocognitive toxicity is characterised by distinct movement symptoms such as bradykinesia, speech disturbances, and gait changes, alongside personality changes, including reduced facial expression, and cognitive deficits such as impaired attention and memory. Regarding the aetiology, reports have found ovement and neurocognitive toxicity to be associated with the presence of CAR-T cells within the blood and CSF.[11] Due to the strong association between CAR-T expansion and the development of movement disorder, several studies have



looked to use prophylactic steroids, such as dexamethasone, if their absolute lymphocyte count in the blood went above a certain threshold; notably, all cases of non-neurotoxicity and non-ICANS were found within the dexamethasone-treated groups.[12,13]

Homing in on another neurologic complication, Graham then spotlighted cranial nerve palsy, which is partial or complete paralysis of one or more of the 12 cranial nerves. It is commonly associated with BCMA CAR-T cell therapy, though less frequently with CD19 CAR-T cells, is found to be early onset following infusion, and can be unilateral or bilateral. Graham recommended, for the management of cranial palsy, a short course of corticosteroids such as prednisolone.

Tumour inflammation-associated neurotoxicity is a localised neurotoxicity following CAR-T cell therapy specifically for CNS tumours, with the exact clinical manifestations dependent on the location of the tumour. As described by Graham, there are different types; Type 1 is linked to signs of raised intracranial pressure, whilst Type 2 is linked to transient worsening of pre-existing neurological symptoms. For Type 1, it is recommended to use CSF diversion, corticosteroids, and hyperosmolar therapy, whilst for Type 2, it is recommended to consider corticosteroids and anakinra.[11]

Myelopathy is most seen with CD19 CAR-T cell therapy, and typically occurs shortly after the onset of ICANS. Symptoms can include flaccid paraplegia, quadriparesis, loss of bladder control, and hypoaesthesia at a sensory level. Regarding management, Graham highlighted high-dose IV steroid treatment, with anakinra considered if there is concomitant ICANS.

Finally, touching on peripheral neuropathy and Guillain-Barré syndrome, these are often described in CD19-directed and BCMA-directed CAR-T cell therapies, with symptoms including back pain, muscle weakness, areflexia, sensory changes, autonomic dysfunction, and respiratory failure. Recommended management includes steroids and high-dose Ig for 5 days.

Fludarabine-associated neurotoxicity is a delayed-onset toxicity linked to high-dose fludarabine-containing regimens. It presents with visual disturbance, dementia, blindness, coma, and even death. Brain MRI may show acute toxic leukoencephalopathy, and management involves corticosteroids and supportive care.

In summary, Graham's talk highlighted the broad spectrum of neurologic complications associated with CAR-T therapy, driven by immune activation, with ICANS as the most prominent toxicity. She emphasised the range of additional complications and the emergence of targeted and prophylactic strategies to mitigate these effects. Overall, she underscored the complexity of CAR-T-related neurotoxicity and the need for tailored management approaches.

BISPECIFIC ANTIBODIES AND OTHER IMMUNOTHERAPIES

Velasco provided a comprehensive overview of the immunotherapy landscape for haematologic malignancies. These include HSCT, monoclonal antibodies, bispecific T cell engagers, antibody–drug conjugates, adoptive cell therapy, immune checkpoint inhibitors, and tumour vaccines.

ICANS is increasingly recognised as an early-onset event of CD3-directed T cell engagers, such as CD19-CD3, CD20-CD3, BCMA-CD3, and GPRC5D-CD3. Notably, blinatumomab, which is directed against CD19-CD3, is associated with the highest incidence of ICANS.[14] Interestingly, compared with BCMA-directed CAR-T cell therapies, bispecific T cell engagers used in multiple myeloma are associated with lower rates of both CRS and ICANS.[15]

Subsequently, moving to immune checkpoint inhibitors, Velasco highlighted that neurological complications are approximately three times more likely to occur in the peripheral nervous system than the CNS. The mechanisms underlying these neurotoxicities are diverse, as she explained, and include T cell-mediated cytotoxicity, humoral autoimmunity, molecular mimicry, and epitope spreading, as well as cytokine-driven inflammation.[16]

Speaking on antibody–drug conjugates, Velasco stressed that those containing vedotin, currently under investigation in haematological malignancies, such as polatuzumab vedotin and pinatuzumab vedotin, are particularly associated with peripheral neuropathy as one of the main adverse events.

In summary, Velasco's talk highlighted the distinct toxicity profiles of immune checkpoint inhibitors, T cell engagers, and antibody–drug conjugates, emphasising differences in dose dependence, predictability, and organ systems affected. She underscored that immune checkpoint inhibitor toxicities are highly variable and unpredictable, whereas T cell engagers and antibody–drug conjugates show more consistent, mechanism-driven adverse event patterns.

NEUROLOGICAL CNS INFECTIONS

Closing the session, Neofytos spoke on some of the most feared neurological infections across immunotherapies: those that infiltrate the CNS. He firstly highlighted bacterial meningitis in allo-HCT recipients, emphasising that it is a rare but serious late post-transplant complication. He highlighted key risk factors such as antibiotic exposure and umbilical cord blood transplants, and noted that common pathogens include *Streptococcus pneumoniae* and *Listeria monocytogenes*.

Neofytos then went on to discuss *L. monocytogenes* meningitis, outlining its epidemiology as an uncommon but notable post-transplant infection, often occurring months after transplant, with CNS involvement in approximately a third of cases. He reviewed its varied clinical presentation, diagnostic challenges, and the key risk factor of severe lymphopenia, and emphasised standard treatment approaches including ampicillin-based therapy, often in combination with gentamicin. He highlighted a 2024 study[17] that demonstrated that *L. monocytogenes* infections in transplant recipients, identified across 111 centres in 30 countries with 41 cases between 2000–2021, remain rare but serious, with an incidence of 49.8 per 100,000 in allogeneic and 13.7 per 100,000 in autologous transplant recipients; most

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patients presented with fever (39%), headache (22%), and gastrointestinal or neurological symptoms, 37% developed bacteraemia, 27% had neurolisteriosis, and overall mortality reached 17%, rising to 27% among those with CNS involvement.

He then highlighted that viral meningoencephalitis after allo-HCT is a rare complication, most often due to herpesviruses, particularly HHV-6, which accounts for 70–80% of cases, typically occurring early post-transplant and commonly presenting with confusion, amnesia, and seizures in patients.

When discussing meningitis, Neofytos emphasised that in allo-HCT recipients, a low clinical threshold is essential due to often subtle presentations, requiring a structured diagnostic workup including early brain imaging (preferably MRI), lumbar puncture with comprehensive CSF analysis, and multiplex PCR (e.g., John Cunningham virus, Epstein-Barr virus, cytomegalovirus, HHV-6, adenovirus), and blood tests such as cultures and cryptococcal and pneumococcal antigens, alongside careful consideration of transplant-specific risk factors and exposures.

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Speaking on brain lesions, he noted that, in allo-HCT recipients, these are rare complications, defined radiologically as focal parenchymal lesions of infectious origin, with fungal pathogens most common, followed by Toxoplasma gondii and bacterial causes, such as the *Nocardia* species.

Addressing fungal brain lesions, Neofytos highlighted that these are rare (<1%) and typically occur more than 6 months post-transplant, most commonly caused by the *Aspergillus* species, followed by other moulds (including *Mucorales*, *Scedosporium*, and *Fusarium*) and *Cryptococcus*. Diagnosis relies on a combination of brain biopsy, CSF analysis (including fungal stain, culture, cryptococcal antigen, galactomannan, β-D-glucan, and PCR), and blood tests, alongside investigations of other infected sites.

Finally, he spoke on cerebral toxoplasmosis in allo-HCT patients. The incidence of this is 1.4%, with clinical presentation occurring within the first 6 months. Neofytos also mentioned norcardiosis, which is the most frequent bacterial brain lesion in allogeneic transplant patients, presenting as a rare, late complication. He highlighted that there are multiple different species of *Nocardia* with varying susceptibility profiles, making it difficult to recommend an empirical therapy.[17]

In summary, Neofytos' talk emphasised the spectrum of CNS infections in immunocompromised patients, highlighting their rarity but significant clinical impact. He outlined key CNS pathogens, including bacterial, viral, fungal, and parasitic causes, alongside their distinct timelines and risk factors, and stressed the diagnostic challenges due to subtle presentations.

Overall, he underscored the importance of early recognition and a structured, CNS-focused diagnostic approach to improve outcomes.

CONCLUSION

Overall, the session highlighted the breadth and complexity of neurological complications across allo-HCT, CAR-T therapy, and other immunotherapies, spanning infectious and immune-mediated causes. From ICANS and movement disorders to CNS infections, the talks emphasised both shared mechanisms and therapy-specific risks. A consistent theme was the challenge of diagnosis and management, reinforcing the need for vigilance, evolving guidelines, and multidisciplinary collaboration to improve neurological outcomes in this setting.

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