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Perspectives

Cutaneous T-cell lymphoma care across Europe: insights from the HORIZON programme

Cutaneous T-cell lymphoma (CTCL) stands out as a rare group of non-Hodgkin lymphomas, primarily affecting the skin. Unlike more common skin cancers, CTCL presents a unique set of challenges in diagnostics and therapeutics due to its heterogeneity and the absence of standardized approaches.[1–3] The interdisciplinary nature of CTCL management adds complexity, involving dermatologists, haematologists, oncologists and psychologists/palliative care physicians. This results in varied perspectives not only between specialties, but also across centres. The lack of specialized European training programmes for skin lymphoma specialists encourages divergent approaches across specialisms, highlighting an unmet need in the field for a training programme facilitating a multidisciplinary approach to patient care.

The 2023 HORIZON programme aimed to address this gap through clinical and research rotations across five European centres of expertise in CTCL: Birmingham (UK), Leiden (the Netherlands), Minden (Germany), Paris (France) and Turin (Italy). The initiative sought to expose emerging skin lymphoma researchers to diverse diagnostic and therapeutic environments, fostering a collaborative global network. The following report reflects the consensus reached by the rotating candidates (five dermatologists, two haematologists, one pathologist), integrating their collective insights on diagnostics, therapeutics and research methodologies.

During the five rotations, a multifaceted approach was adopted. Participation in multidisciplinary team meetings highlighted the importance of collaborative decision-making in formulating treatment plans for patients with CTCL. Hands-on experience in ultrasound sonography provided valuable insights into one technique that is valuable for identifying and monitoring lymph node status. Exposure to delivery of radiotherapy, including total skin electron beam irradiation, provided practical demonstrations of the therapeutic radiologic interventions in CTCL management. In diagnostics, the flow cytometry laboratory played a pivotal role in characterizing abnormal T-cell populations – a hallmark of CTCL. Advanced techniques such as cytometry time of flight, clonality assays and fluorescence-activated cell sorting augmented the diagnostic repertoire, allowing for high-dimensional analysis and precise isolation of specific cell populations. Multiplex immunofluorescence laser dissection microscopy deepened the understanding of the tumour microenvironment. The incorporation of Oxford Nanopore analysis highlighted a commitment to genomic exploration, shedding light on the genetic underpinnings of CTCL.

Within pathology, the programme delved into histopathology and immunohistochemistry, underscoring fundamental markers for early CTCL diagnosis (CD3, CD4, CD7, CD8, CD30) and their integration with additional ones [CD5, CD56, T-cell receptor (TCR)-β/TCR-γ/TCR-δ, granzyme B, Epstein–Barr virus-encoded RNAs (EBER), Ki67] for advanced cases, such as the intense programmed cell death protein 1 (PD-1)/thymocyte selection-associated high mobility group box protein (TOX) expression of $>50\%$ in Sézary syndrome. Correlating histopathological findings with clinical presentations elucidated the dynamic interplay between cellular changes and overall disease manifestation. Moreover, the exploration of artificial intelligence (AI) underscored the programme's commitment to staying at the forefront of technological advancements in pathology. In terms of blood flow cytometry, uniformity was observed across centres, utilizing classical markers like CD3, CD4, CD8, CD45, CD7, CD26 and CD2.[4] Differences emerged in optional markers, including maturation markers (CD27, CD28, CD45RA, CD45RO, CD19), targetable markers [PD-1, killer cell immunoglobulin-like receptor 3DL2 (KIR3DL2), CCR4] and those related to the adenosine pathway (CD38, CD39, CD73) – highlighting the multitude of research avenues pursued by each centre.[5,6]

Regarding therapies, consistency was noted in adopting both traditional and newer treatments, aligning with the latest European Organisation for Research and Treatment of Cancer (EORTC) guidelines.[5] Established options, including retinoids, phototherapy, radiation therapy and extracorporeal photopheresis, alongside newer choices like chlormethine gel, anti-CCR4 (mogamulizumab) and anti-CD30 (brentuximab–vedotin), were widely used across all centres.[5] The diverse therapeutic approaches observed can be attributed to the introduction of innovative treatments evaluated in clinical trials. An example is the use of the anti-KIR3DL2 lacutamab in France, as the Paris centre played a crucial role in the TELLOMAK trial. Moreover, the availability of romidepsin varied by country, while resminostat was featured in the RESMAIN trial across all the five centres.[5] Alongside interventional trials, the PROCLIPI study is a global study prospectively collecting information to develop a prognostic index to better identify patients at risk of progression for improved management.[7]

Perhaps the most significant difference between centres was the involvement of clinical nurse specialists, particularly in the UK. This group of highly skilled health professionals represents a significant opportunity for holistic and comprehensive patient-centred care.

The programme's unique teaching approach has not only enriched the understanding of CTCL, but has also laid the groundwork for a collaborative network to drive advancements in research. At present, two projects are underway: one is dedicated to harnessing AI to assist in the histological diagnosis of early mycosis fungoides, while the other is investigating the role of the cutaneous microbiome in the progression of CTCLs. As the initial HORIZON programme concludes, the role of the EORTC cutaneous lymphoma

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working group becomes crucial in mentoring young skin lymphoma trainees and forging the path ahead. A second programme is planned in 2025 for new skin lymphoma enthusiasts; further information is available at the EORTC website.[8]

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