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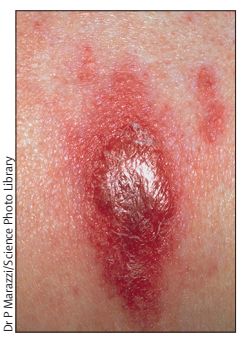
Anti-KIR3DL2 therapy in the treatment of Sézary syndrome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In *The Lancet Oncology*, Bagot and colleagues[1] present the results of an international, multicentre, open-label, phase 1 study evaluating IPH4102 in patients with relapsed or refractory cutaneous T-cell lymphoma. IPH4102 is a humanised, first-in-class, monoclonal antibody that targets KIR3DL2, a cell surface protein widely expressed in cutaneous T-cell lymphoma, and predominantly in its leukaemic form, Sézary syndrome. The binding of the drug with the target induces antibody-dependent cell cytotoxicity and phagocytosis.[2]

The study was composed of two parts (a dose-escalation and cohort expansion) with different inclusion criteria. Eligible patients for the dose-escalation stage had relapsed or refractory cutaneous T-cell lymphoma of stage IB or higher after at least two previous systemic therapies, and with at least 5% of skin-infiltrating mononuclear cells or phenotypically aberrant circulating T-cells expressing KIR3DL2. However, KIR3DL2 expression was not an inclusion criterion for cohort expansion, which included patients in two disease subsets, Sézary syndrome or mycosis fungoides, with evidence of large-cell transformation. The choice of Sézary syndrome is related to the finding that KIR3DL2 is expressed in more than 85% of patients with Sézary syndrome, whereas its expression in mycosis fungoides is more heterogeneous.[3] All patients in the cohort expansion received a flat intravenous dose of 750 mg IPH4102.

The key messages of this study are the favourable safety profile of the drug (primary endpoint), coupled with potentially relevant clinical activity. Most common adverse events were grade 1 or 2 (peripheral oedema in 12 [27%] of 44 patients; and fatigue in nine [20%] patients). Six grade 3 or 4 treatment-related adverse events were described, of which three were grade 3 lymphopenia. One death due to hepatitis occurred in a patient 6 weeks after treatment discontinuation due to progression in association with human herpe svirus 6B liver infection. With regard to clinical activity, the treatment induced substantial responses in 35 patients with Sézary syndrome; 15 (43% [95% CI 28·0–59·1]) achieved a global overall response, the proportion who achieved an overall response in the blood was 19 (56%) of 34, and median response duration was 13·8 months (IQR 7·2–not reached).

Sézary syndrome represents the erythrodermic and leukaemic variant in the spectrum of cutaneous lymphomas, accounting for 2% of all cases, with a poor prognosis and a disease-specific survival of 36% at 5 years.[4] The treatment of Sézary syndrome remains a challenge in terms of responses to treatment, response duration, side-effects, and impairment of the quality of life; thus, these patients have a high clinical need for effective treatments.

According to the European Organisation for Research and Treatment of Cancer guidelines,[5] first-line treatments for Sézary syndrome are extracorporeal photochemotherapy alone or in combination, low-dose methotrexate, and chlorambucil plus prednisone, and second-line approaches include chemotherapy (gemcitabine and pegylated liposomal doxorubicin), alemtuzumab, and allotransplant. Allogeneic stem-cell transplantation represents the only therapy with curative intent in cutaneous T-cell lymphoma, although it is associated with relevant treatment-related morbidity and mortality and warrants a careful patient selection.

The retrospective multicentre analysis of 853 advanced-phase patients with Sézary syndrome or mycosis fungoides done by the Cutaneous Lymphoma International Consortium[6] highlighted that these patients have a great heterogeneity of treatment approaches (more than 20 different therapeutic methods with 36% of patients receiving four or more treatment lines). Extracorporeal photochemotherapy alone or in combination with immune modulators or retinoids was the most frequent treatment in erythrodermic cutaneous T-cell lymphoma and patients with Sézary syndrome. Chemotherapy as first line treatment was found to be associated with a significantly increased risk of death or

therapy change, meaning that other approaches should be preferred as first-line therapy.

Numerous studies have analysed the clinical activity of extracorporeal photochemotherapy in patients with cutaneous T-cell lymphoma, although the majority are retrospective or single-centre and include relatively small patient cohorts. The proportions of patients achieving a response range between 33% and more than 90%, with mean values of 63% with complete responses in about 20% of cases.[7]

Two randomised studies[8,9] have documented the clinical efficacy of new drugs brentuximab vedotin and mogamulizumab in pretreated patients with cutaneous T-cell lymphoma. In the ALCANZA trial,[8] a randomised phase 3 trial comparing brentuximab vedotin versus methotrexate or bexarotene in CD30-positive mycosis fungoides or primary cuta-neous anaplastic large-cell lymphoma, patients with high blood Sézary cell counts were not included; however, the clinical activity of brentuximab vedotin has been reported in patients with Sézary syndrome in previous phase 2 studies. In the MAVORIC trial,[9] a phase 3 randomised trial comparing the anti-CCR4 antibody mogamulizumab with vorinostat, the proportion of patients with a response in the blood was 68% and global responses in Sézary syndrome occurred in 30 (37%) of 81 patients. The median duration of response in the blood was 25·5 months (IQR 15·9–not estimable) and in the skin 20·6 months (11·2–not estimable), with 36 (20%) of 184 patients developing serious adverse events considered treatment related.

The results reported by Bagot and colleagues[1] in this phase 1 study of IPH4102 are encouraging. However, they need to be confirmed in phase 2 and 3 trials, together with the identification of parameters associated with a better clinical activity that could drive patient selection. Future studies could also attempt to ascertain the position of this treatment in the treatment of patients with Sézary syndrome. At the moment, we could speculatively adopt this targeted approach in patients refractory to, or who have relapsed after, extracorporeal photochemotherapy, but also in association with it or even before, particularly in patients with a large tumour burden in the peripheral blood who are less responsive to standard therapies. Moreover, similarly to mogamulizumab, IPH4102 could also be considered as a bridge to allo transplant in young candidate patients.

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I have participated in the advisory boards of Takeda, Kiowa Kirin, Therakos, Actelion, Helsinn, Innate Pharma, and 4SC.

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Of microbes and women: *BRCA1*, vaginal microbiota, and ovarian cancer

The human body is home to several niche-specific microbial communities (termed microbiota), which, through host–microbe networking, are thought to have an integral role in human physiology. Many observational studies have shown differences in terms of the composition of bacterial microbiota (and much less frequently of viral and fungal microbiota) between healthy people and those presenting with various

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