Background
Aggressive B-cell and T-cell lymphomas constitute a substantial proportion of all human malignant Non-Hodgkin lymphomas (NHL) and pose an important clinical challenge. Given the fact that these lymphomas frequently develop resistance to chemotherapy and are associated with high relapse rates, pre-clinical PDX models could provide a valuable tool to understand the molecular mechanisms leading to treatment failure.

We have received four patient tumour tissue samples from aggressive NHLs, two of which were diffuse large B-cell lymphoma (DLBCL) samples from the peripheral blood and two were Burkitt lymphoma samples from fine needle biopsies. We successfully established PDX models and in parallel PD3D models from these tumours.

Methods
The patient-derived tumours were transplanted subcutaneously into immune-deficient NOD scid gamma mice. Within 80 days, palpable tumours were grown and passed via the same route to immune-deficient NMRI nu/nu mice. Around after five passages, these lymphoma models were used in a chemosensitivity assay. When the tumour volume reached > 0.1 cm³, treatment with cyclophosphamide, vincristine, rituximab and gemcitabine was started. For the establishment of PD3D, primary cell suspension (one of each type of NHL) was seeded on a Matrigel layer and was grown for at least two weeks. For chemosensitivity testing, lymphoma spheroids from single cell suspension were formed during four days and subsequently treated with vincristine for eight days at different concentrations.

Results

Immunohistochemistry & Chemosensitivity

3D cell culture

Conclusions

We successfully established four PDX models with solid NHL-tumours on immune-deficient mice as well as the corresponding PD3D models. Both model systems are reproducible. The best inhibition on tumour growth resulted from treatments with gemcitabine, cyclophosphamide and vincristine as monotherapy in all four NHL-PDX models. Those responses are clinically considered as partial up to complete remission and reflect the clinical situation.

However, in the clinic the NHL were treated by CHOP therapy (cyclophosphamide, doxorubicin, vincristine and prednisone combined) with and without rituximab (R-CHOP). In our chemosensitivity assays, only the model DLBCL Ly12318 partially positive for hCD20 showed a response to rituximab whereas both Burkitt lymphomas, strong hCD20 positive, did not show any response to rituximab. These results indicate that a single treatment with rituximab did not reduce the tumour growth and/or that a resistance to rituximab was developed.

Regarding the PD3D models, the efficacy of vincristine as monotherapy correlates with the results from the chemosensitivity in immune-deficient mice. These preliminary findings indicate that our NHL-PDX models can be supported by PD3D to investigate cellular and molecular mechanism of drug sensitivity and resistance, thereby providing a valuable pre-clinical tool for developing new therapeutic approaches. In further chemosensitivity assays, the clinical treatment of CHOP and R-CHOP on NHL-PDX in comparison to NHL-PD3D will be tested.

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