Intracerebral Human Lymphoma – An Experimental Model*

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Primary central nervous system lymphomas are rather rare, however, their frequency seems to be increasing in both high risk and immunocompetent patients with very poor prognosis. Here we describe a model intracerebrally xenotransplanting human non Hodgkin lymphoma cells of B cell origin (HT 58). This offers a unique possibility to study the therapeutic response, especially on systemic treatment. Briefly, one million lymphoma cells grew as meningeal tumor mass, infiltrating the brain directly as well as via the perivascular space. The lymphoma cells preserved all the phenotypic characteristics of the source tumor. (Pathology Oncology Research Vol 2, No3, 174–176, 1996)

Key words: lymphoma, CNS, tumor-model

Introduction

Primary central nervous system lymphoma (PCNSL) is a relatively rare tumor, representing approximately 1% of all non-Hodgkin lymphomas and 1% of primary brain tumors. In the past decade, the incidence of PCNSL increased both in high risk groups (immunocompromised, AIDS) and in the general population. Usually they have B cell origin and appear as large cell variants of high grade lymphoma. It is still unknown what factor(s) are responsible for the accumulation of lymphoid cells in the CNS (neither contribution of EBV, nor special molecular/genetic changes were proved). The prognosis is poor (worse than that of systemic NHLs); surgery is not a real therapeutic choice, radiation alone can cause high complete response but the early recurrence is also high. It is still a hope that a combined therapy which includes a more effective chemotherapy could improve survival. Since chemotherapy of CNS tumors requires a special approach, especially in case of systemic treatment, we tried to introduce a xenograft model for studying the therapeutic response of PCNSL.

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Materials and Methods

Cell lines

3LLT-HH cells (a selected variant of 3LLT with increased metastatic capacity, especially into the liver) were isolated from liver metastasis and suspended in RPMI 1640 medium. HT 58 human B lymphoma cells were collected from in vitro culture. (The phenotype of the HT 58 cells: IgM, IgD, CD10, CD19, CD20, CD38, CD45, CD3, CD4, CD5, CD7, CD8, CD14, CD33, CD34.) 3LLT-HH cells were injected into inbred C57Bl mice, and HT 58 cells into artificially immunosuppressed inbred CBA/Ca mice.

Intracerebral injection

The injected volume was 0.05 ml which contained either the medium (for controls) or tumor cells: 1.5-4.0 x 10⁵ 3LLT-HH cells; or 0.5-1.0 x 10⁶ HT 58 lymphoma cells. The mice were under ether narcosis when intracerebral injection was performed on the right side, at one-third of the distance between the eye and the ear. The intended depth was 0.5 mm, controlled by a piece of hard rubber. At least 10 mice were used per experimental group.

Experimental end points

Beside introducing the technique, the experiments aimed to develop a system suitable for future therapeutic studies. Therefore, survival was followed and partly the
Results and Discussion

Fig 1 shows that all 3LLT-HH injected mice died within 10 days, depending on the number of cells injected intracerebrally. (With a little practice, no mice were lost due to technical failure.) Extracerebral metastasis, lung metastases, were found in 2 recipients (given the higher dose). As expected, the HT 58 injected mice lived much longer. All of them died after the injection of 10⁶ cells, while 3/10 survived 5x10⁵ cells. This indicates that at least one million HT 58 cells are required to establish an experimental system for therapeutic studies.

Figure 1. Survival curves of mice receiving intracerebral injection of 3LLT-HH or HT 58 human B cell lymphoma.

extension and characteristics of tumor progression for all recipients was checked by autopsy, as well as by histology of the brain, lung and liver. Other suspected tissues were examined if necessary.

Figure 2. Massive meningeal infiltration with HT 58 lymphoma cells. HE

Figure 3. Common route of invasion: perivascular spread of HT 58 lymphoma cells. HE

Figure 4. Periventricular cuff of HT 58 lymphoma cells. HE

All mice died due to the tumor as, there was no sign of infection. Macroscopically, usually, the slight enlargement of the right hemisphere and an opaque area at the injection site suggested the presence and consequence of the tumor. Histology proved that HT 58 cells grew very actively, producing leptomeningeal invasion (Fig 2). There were many mitotic and some apoptotic figures, and the lymphoma cells showed the same phenotypic profile (including lambda light chain monoclonality) as was observed in the in vitro or in vivo subcutaneously growing variants. The tumor cells invaded the brain relatively easily, producing random fingerlike patterns. The perivascular and periventricular proliferation was very characteristic. (Fig 3 and 4). Similarly to the in vitro HT 58 cell line, the intracerebral lymphoma preserved TGF-β expression on the cell surface, although in normal circumstances TGF-β is a potential inhibitor of lymphoid cell proliferation.

In the past there have been several attempts to study intracerebrally injected human lymphoblastoid or lymphoma cells in xeno-(hetero-)transplanted mice. In another study intracranial challenge with in vitro cultured brain tumor cells (medulloblastoma and glioma) has been made in order to use the system to assess the effect of various chemotherapeutic agents given intraperitoneally.
One of the advantages of our lymphoma model is the similarity to the human clinical situation. The disadvantage is obvious. We can use only the survival time as the end-point in therapeutic experiments. However, the survival of the treated individual is still the most informative parameter in the evaluation of any antitumor effect.

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References