Abstract

Currently, adjuvant chemotherapy for glioblastoma patients can prolong survival time relative to patients who receive only surgery and radiotherapy. Despite these improvements and experimental and clinical efforts to improve the prognosis for glioblastoma patients, it remains poor. At present, interest is focused on individual prognostic factors influencing patient responses to therapy. Photodynamic therapy may be a promising therapeutic option in the treatment of glioblastoma. In this investigation we examined whether uptake of hypericin (HY), a fluorescent photosensitization agent, by ex vivo glioblastoma cell lines correlates with prognosis of the individual from which the cell lines were derived. Twelve primary human glioma cell cultures were incubated with 20 μmol HY. Fluorescence intensity was measured using fluorescence microscopy. Three patients suffered from an anaplastic astrocytoma, WHO grade III, nine had a glioblastoma, WHO grade IV. In 6/12 patients complete tumour resection was possible. The mean survival time of the six patients in whom complete tumour resection was performed was 26 months, compared with 5 months for those who
underwent incomplete resection. Eleven patients received radiation therapy. The five patients who received chemotherapy survived for a mean duration of 26 months, compared with the seven patients who survived for a mean duration of 5 months without chemotherapy. Statistical analysis using a parametric survival model based on the Weibull distribution showed that fluorescence intensity was the variable with the lowest p-value associated with survival ($p = 0.0225$). An increase of 553 arbitrary units of fluorescence intensity is predicted to double survival time. Uptake of HY, a lipophilic molecule, is assumed to be related to low-density lipoprotein (LDL) uptake and metabolism. Cell proliferation is associated with a high turnover of cholesterol and membrane growth, which is related to cholesterol uptake by LDL. In summary, HY uptake by ex vivo glioblastoma cell cultures seems to be positively associated with survival of patients with malignant glioma.

**Keywords:** Hypericin; Photodynamic therapy; Glioblastoma; Prognosis

**Article Outline**

1. Introduction
2. Methods and patients
   2.1. Cell cultures
   2.2. Statistical analysis
3. Results
4. Discussion
References

**Note to users:** The section "Articles in Press" contains peer reviewed accepted articles to be published in this journal. When the final article is assigned to an issue of the journal, the "Article in Press" version will be removed from this section and will appear in the associated published journal issue. The date it was first made available online will be carried over. Please be aware that although "Articles in Press" do not have all bibliographic details available yet, they can already be cited using the year of online publication and the DOI as follows: Author(s), Article Title, Journal (Year), DOI. Please consult the journal's reference style for the exact appearance of these elements, abbreviation of journal names and the use of punctuation.

There are three types of "Articles in Press":

- **Accepted manuscripts:** these are articles that have been peer reviewed and accepted for publication by the Editorial Board. The articles have not yet been copy edited and/or formatted in the journal house style.
- **Uncorrected proofs:** these are copy edited and formatted articles that are not yet finalized and that will be corrected by the authors. Therefore the text could change before final publication.
- **Corrected proofs:** these are articles containing the authors' corrections and may, or may not yet have specific issue and page numbers assigned.