Expression of the active caspase-3 in children and adolescents with classical Hodgkin lymphoma

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SUMMARY

The aim of the study was to determine whether the expression of active caspase-3 in neoplastic Hodgkin and Reed-Sternberg (H/RS) cells correlates with the treatment response and provides prognostic information on treatment outcome. In this retrospective study, we included 56 patients with classical Hodgkin lymphoma treated at the Department of Paediatric Haematology and Oncology between January 2000 and June 2005. Active caspase-3 was detected by immunohistochemistry in primary biopsy specimens. Seventeen patients (29.3%) were evaluated as caspase-3 positive and remained alive in the first complete remission. This stood in contrast to patients with less than 5% caspase-3 positive cells, five of whom experienced relapse and three patients died. Adequate treatment response was achieved in 11 patients (19.6%). Comparison of event-free survival with regard to the percentage of caspase-3 positive tumour cells showed a tendency for a better clinical outcome in patients with 5% or more active caspase-3 positive cells.

Keywords: classical Hodgkin lymphoma – apoptosis – active caspase-3 – therapy response – clinical outcome

Exprese aktivní kaspázy 3 u dětí a adolescentů s klasickým Hodgkinovým lymfomem

SOUHRN

Cílem naší studie bylo zjistit, zda exprese aktivní kaspázy 3 v buňkách Hodgkinových a Reed-Sternbergové koreluje s dosaženou léčebnou odpovědí a poskytuje prognostickou informaci ohledně léčebného výsledku. Do retrospektivní studie jsme zařadili 56 pacientů s klasickou formou Hodgkinova lymfomu, kteří byli léčeni na Klinice dětské hematologie a onkologie v období mezi lednem 2000 a červnem 2005. Aktivní kaspáza 3 byla detekována imunohistochemicky ve vzorcích z primárních biopsiích. Sedmnáct pacientů (29,3%) bylo hodnoceno jako kaspáza 3 pozitivních, všichni žijí v první kompletní remisi onemocnění. Oproti tomu ve skupině pacientů s méně než 5% kaspáza 3 pozitivních HRS buněk jsme diagnostikovali v pěti případech relaps onemocnění a tři nemocní v důsledku tohoto onemocnění zemřeli. Adekvátní léčebné odpovědi dosáhlo 11 pacientů (19,6%). Při hodnocení event-free survival s ohledem na zastoupení kaspáza 3 pozitivních nádorových buněk jsme ukázali tendenci k lepšímu klinickému průběhu u nemocných s více než 5% buněk s pozitivitou aktivní kaspázy.

Klíčová slova: klasický Hodgkinův lymfom – apoptóza – aktivní kaspáza 3 – léčebná odpověď – klinické výsledky

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Classical Hodgkin lymphoma (cHL) is a systemic lymphoproliferative disorder derived typically from pre-apoptotic germinal centre B-lymphocytes but rarely from transformed T-cells (1-4). Combined modality treatment (multidrug chemotherapy regimens, radiotherapy) has improved the outcome of cHL patients, with a 5-year overall survival of 90 % (5). Therefore, the aim of current treatment protocols is to individually tailor the therapy to specific risk factors (clinical and biological prognostic factors including caspase-3 (6,7)) with a reduction of late treatment-related complications and maintenance of high cure rates (8,9).

Chemotherapeutic approaches are based on proper activation of an apoptotic pathway and the consequential activation of effector caspase-3. In some cases of Hodgkin lymphoma, chemotherapy resistance can be caused by ineffective or functionless execution or progression of the apoptotic cascade in neoplastic cells.

Apoptosis, as a pathway of programmed cell death, is a result of a complex activation of various molecules including caspases (cysteine-containing aspartic acid-specific proteases). Caspases are present in the cytoplasm of both normal and neoplastic cells. Their activation includes the cleavage of two different inactive subunits and formation of a functional tetramer. Caspases are divided into two groups: initial caspases (caspase 2, 8, 9 and 10) and effector caspases (caspase-3, 6 and 7). Activation of initial caspases is provided either by T-lymphocytes reacting with a cell membrane death receptor (Fas/CD95) or by cytotoxic stress via releasing intracellular cytochrome *c*. Active initial caspases react with effector caspase proenzymes. Effector caspase-3 is pres-

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