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特集
臨床試験から得られた外科治療のエビデンス

総説
標的アイソトープ治療の現状と将来展望

Current Organ Topics
肝・胆・膵癌 外科切除における Surgical Margin, R0・R1 の臨床的課題

特別寄稿
第39回 癌免疫外科研究会

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已發表於美國腫瘤醫學期刊

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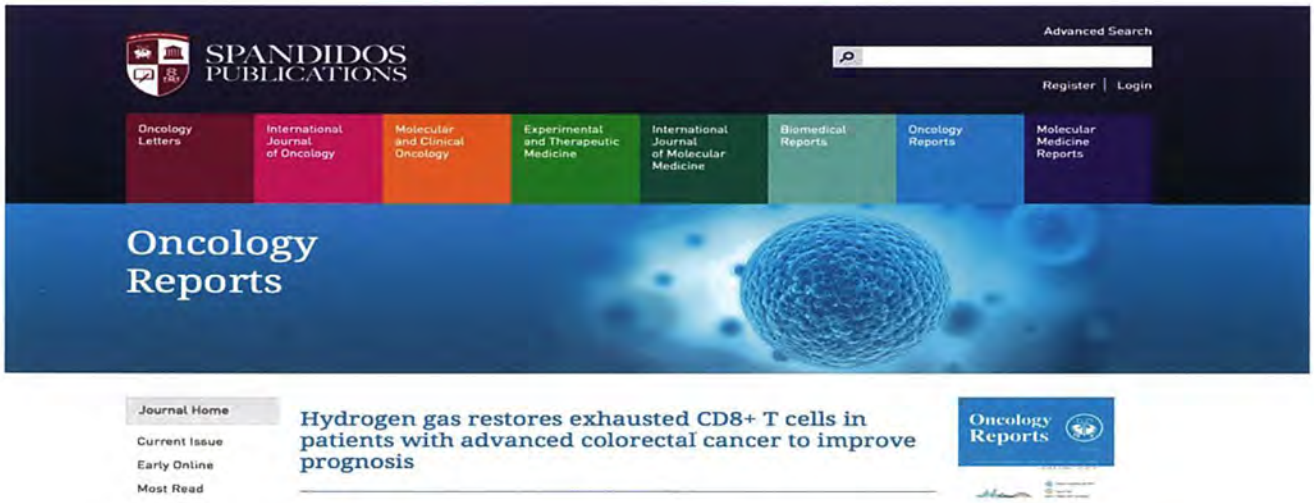
Effects of hydrogen gas on exhausted CD8$^+$ T cells (PD-1-positive, terminally differentiated CD8$^+$ T cells).

Background: CD8$^+$ T cells progress from an early-differentiated (early-CD8$^+$ T cells) to a terminally differentiated state (terminal-CD8$^+$ T cells). PD-1 expression is rapidly upregulated in antigen-activated T cells, and rapidly downregulated when the antigen is cleared. In the presence of persistent antigen stimulation, such as that in cancer patients, PD-1 expression is not downregulated and terminal-CD8$^+$T cells become exhausted. **Methods:** Using flow cytometry, we investigated PD-1 expression in CD8$^+$T cells in the peripheral blood of 37 patients with stage IV cancer, before and after they received hydrogen gas treatment. We analyzed associations between treatment and progression-free survival (PFS) using Cox and Kaplan-Meier survival analyses. **Results:** Treatment lead to partial response (PR) in 12 patients and stable disease (SD) in 14 patients, with response rates of 32.4% and 37.8%, respectively (with an overall clinical response rate of 70.3%), and reduced the number of PD-1-positive, terminal-CD8$^+$ T cells in 9 of 12 patients with PR (75%) and in 8 of 14 patients with SD (57%). However, in 8 of 11 patients with progressive disease (PD) (72.7%), these cell counts increased. Multivariate analyses demonstrated that higher PD-1-positive, terminal-CD8$^+$ T cell counts were associated with shorter PFS periods, both before (hazard ratio [HR] = 3.23; 95% confidence interval [CI], 1.475–7.070; $p = 0.003$) and after (HR = 2.75; 95% CI, 1.273–5.951; $p = 0.01$) treatment, although the hazard ratio was decreased by treatment. Additional analysis showed that patients with higher PD-1-positive, terminal-CD8$^+$ T cell counts had shorter survival rates than those with lower counts, both before and after treatment (log rank test, $p = 0.001$ and $p = 0.005$, respectively). The 20-month survival rates for patients with higher PD-1-positive, terminal-CD8$^+$T cell counts improved from 0% to 36.7% after treatment. **Conclusions:** These results suggest that PD-1-positive, terminal-CD8$^+$ T cell counts are highly associated with PFS duration in patients with stage IV carcinomas, and hydrogen gas treatment contributes to clinical outcomes by reducing PD-1-positive, terminal-CD8$^+$ T cell counts.

已發表於英國腫瘤醫學期刊



Abstract

Exhausted cluster of differentiation (CD)8+ T cells lose immunological activity due to mitochondrial dysfunction caused by peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) inactivation, resulting in a poor prognosis in patients with cancer. As hydrogen gas was recently reported to activate PGC-1α, the present study investigated whether it restores exhausted CD8+ T cells to improve prognosis in patients with stage IV colorectal cancer. A total of 55 patients with histologically and clinically diagnosed stage IV colorectal carcinoma were enrolled between July 2014 and July 2017. The patients inhaled hydrogen gas for 3 h/day at their own homes and received chemotherapy at the Tamana Regional Health Medical Center (Tamana, Kumamoto, Japan). The CD8+ T cells were isolated from the peripheral blood and their phenotype was analyzed by flow cytometry. It was found that exhausted terminal programmed cell death 1 (PD-1)+ CD8+ T cells in the peripheral blood are independently associated with worse progression-free survival (PFS) and overall survival (OS). Notably, hydrogen gas decreased the abundance of exhausted terminal PD-1+ CD8+ T cells, increased that of active terminal PD-1- CD8+ T cells, and improved PFS and OS times, suggesting that the balance between terminal PD1+ and PD1- CD8+ T cells is critical for cancer prognosis. Therefore, a novel system for patient classification (category 1-4) was developed in the present study based on these two indices to assist in predicting the prognosis and therapeutic response. Collectively, the present results suggested that hydrogen gas reverses imbalances toward PD-1+ CD8+ T cells to provide an improved prognosis.