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Effect of treatment of tumor-infiltrating lymphocytes on gastric cancer

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Abstract

AIM: To study the effect of immune treatment on gastric cancer.

METHODS: Thirteen patients with advanced gastric cancer were given TIL adoptive immunotherapy in this study. Histological findings showed that 13 patients had gastric adenocarcinoma. Patients received operations on their primary tumor, which could not be resected. Small tumor tissue and metastic lymph nodes were got during the operation for TIL preparation. Ten patients were treated as control group. During TIL treatment, the patients did not received any other treatment. Surgical speciments (metastatic lymphnodes) with pathological diagnosis were obtained from operating room. The lymph nodes were minced and dissociated in RPMI 1640 with 0.03% hyaluronidase typeⅤ (1500 U/g), 0.05% collagenase type Ⅳ (200 U/g), and 0.008% deoxyribonuclease type Ⅰ (100 U/g) (Sigma, United States) at 37 ℃ for 12 h. The cell mixture was then filtered through 4-layer gauge, washed twice in Hank's and separated on Ficoll-Hypague (Shanghaiist Chemical Reagent Factory) at 900 × *g* for 20 min. Finally, the cells were harvested and counted. Cells suspension containing TIL and tumor cells were extensively washed and resuspended at a final concentration of 106 lymphocytes/mL in complete medium containing 15% human AB serum, 100 U/mL penicillin and 100 μg/mL streptomycin in RPMI 1640 (Gibco). The final concentration of rIL-2 (Military Medical Institute, Nanjing) was 500 U/mL. Cultured after 3-4 d, lymphoid cells were counted and culture was separated into more flasks when the concentration of lymmphoid cells reached or exceeded 2 × 10^6 /mL until the total amount reached about 5 × 10^9/mL cells. Cytotoxic activities of TIL were tested by 6 h ^{51}Cr-release assay.Target cells (5 × 10^5/mL) (human gastric adenocarcinoma) in 1 mL of culture medium were labelled with 100 μci of $Na_2{}^{51}CrO_4$ (Beijing Atomic Energy Research Institute, Beijing), washed and adjusted to 10^5 cells/mL. Labelled cells (E/T: 50:1, 25:1 and 12.5:1) were seeded in round-bottom micro test plates (Corning, Japan) at 104 cells/well. Isotope release was measured in a gamma counter (Packard, United States). The percentage of cytotoxicity was calculated according to the following formula: Cytotoxicity% = (Experimental-Spontaneous)/(Maximum-Spontaneous) × 100. Target cells without effective cells were mixed with 0.1 mL of culture media to obtain spontaneous release, and with 0.1 mL of 0.1 mol/L HCl to obtain maximum ^{51}Cr release. TIL cells so induced were counted, washed twice, resupended in 100 mL 0.9% NaCl solution and intravenouslly transferred. The number of total autologous TIL cells injected was more than 5 × 10^9 cells for one patient and usually separated into 2-3 injection during the treatment, rIL-2 5000 U/d (Nanjing Military Medical institute, Nanjing) in 2 mL of 0.9% NaCl solution was intramuscularly injected starting from 5 d before TIL cells transfer to 5 d after transfer of TIL cells. All patients were given scheduled gastric roentgenograms. CT scanning, B type ultrasound, histological examination and immune function were used to observe the changes before, during and after treatment. The curative effects were judged by the standard of WHO. The methods of the assays of SIL-2R, NK cytotoxi city and CD4/CD8 were carried out respectively according to the references.

RESULTS: The Nk cytotoxicity and CD4/CD8 were significantly increased ($P < 0.01$) after 3-6 mo treatment. The soluble IL-2 receptor in sera of patients was significantly decreased ($P < 0.01$) after 3-6 mo treatment. There were no significantly differences in the test of CD4/CD8, the cytotoxicity of Nk cells and the soluble IL-2 receptor in serum between the group before treated by TIL and the control group ($P > 0.05$). The NK cytotoxicity and CD4/CD8 in patients treated by TIL were significantly more than those in the control group. On the contrary, the soluble IL-2 receptor in serum of patients treated by TIL was significantly less than those in serum of the control group. The patients of control group survive d from 4-5 mo to 9 mo (less than one year) after operation. However seven of the thirteen patients treated by TIL after operation survived over one year. Appetite was improved, sinew enhanced, weight increased and pain relieved in most of patients treated by TIL. On the contrary, the symptoms and signs of patients of control group were not improved. According to the standard of WHO, there were significantly differences of PD (Disease Progress), MR (Minor remission), and PR (partial remission) between TIL group and control group. The results indicated that tumor focus completely disapeared in 1 (80%) of 13 patients, significantly decreased in 4 (30%) of 13 patients and slightly decreased in 7 (53%) of 13 patients, suggesting that the treatment of TIL in the patients with advanced cancer was effective. No side effects were found except for transient fever in 2 patients.

CONCLUSION: TIL should be one of the fundamental therapies for the advanced gastric cancer, it can regulate the balance of immunity, relieve pain, improve symptoms and signs and prolong survival time.

Key words: Stomach neoplasms; Tumor infiltrating lymphocyte; Interlukine-2; Immunotherapy

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