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Abstract

Cancer patients who have many tumor infiltrating lymphocytes (TIL) tend to have better prognoses. A relationship between prognosis and TIL or regional lymph node response is present in several malignant diseases. TIL are mainly T lymphocytes, as ascertained by immunological methods. Results of studies on T-lymphocyte subsets comprising TIL using monoclonal antibodies (OKT series and Leu series) are summarized in this review.

KEYWORDS: tumor infiltrating lymphocytes(TIL), lymph node reaction, cell mediated immunity, monoclonal antibodies, local administration of immunomodulator

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INDENTIFICATION AND PROGNOSTIC IMPLICATIONS OF TUMOR INFILTRATING LYMPHOCYTES — A Review —

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Abstract. Cancer patients who have many tumor infiltrating lymphocytes (TIL) tend to have better prognoses. A relationship between prognosis and TIL or regional lymph node response is present in several malignant diseases. TIL are mainly T lymphocytes, as ascertained by immunologiccal methods. Results of studies on T-lymphocyte subsets comprising TIL using monoclonal antibodies (OKT series and Leu series) are summarized in this review.

Key words : tumor infiltrating lymphocytes (TIL), lymph node reaction, cell mediated immunity, monoclonal antibodies, local administration of immunomodulator.

The prognosis of cancer patients tends to be better if TIL are numerous than if they are few. This phenomenon was first reported in malignant melanoma (1), and has since been confirmed in other cancers (2). Lymphocytes and plasma cells are among these infiltrating cells. The former have been studied more extensively than the latter. The majority of the lymphocytes have been identified to be T lymphocytes by immunological methods (3). More recently, monoclonal antibodies of the OKT and Leu series have been employed to differentiate the T-cell subsets (4). Intratumoral administration of immunomodulators results in enhanced TIL and antitumor activity in the regional lymph nodes.

TIL and Prognosis

Lymphocytes infiltration in tumor tissue was first recognized as an immune reaction in cancer bearing hosts (1, 5). Subsequently, studies have been undertaken to ascertain the relationship between these cells and the prognosis of cancer (4). Black *et al.* (7) systematically evaluated the prognosis of gastric cancer in the presence of different numbers of TIL on a 5-grade scale from 0 to 4. Prognosis was significantly more favorable in the presence of large numbers of TIL. The five year survival rate was good in cases with numerous TIL, especially in advanced cancers. In cancer of the uterine cervix, most reports have linked the presence of many TIL with a favorable prognosis and infrequent regional lymph node metastasis.

TIL also is seen in breast cancer in the absence of inflammatory changes. In the medullary type of cancer, which accounts for 5 percent of all cases and is associated with large numbers of TIL, the prognosis is good (8). Black *et al.* (9) found that 9 of 11 patients showing high counts of TIL even when they had regional axillary lymph node metastases survived twice as long as the patients without TIL. It also has been reported that prognosis is good in cases with marked round cell infiltration of breast cancers exceeding 4 cm in diameter (10), although contrary data has been reported (11).

Response of Regional Lymph Nodes

The relationship between regional lymph node response and prognosis also has been investigated. Studying gastric cancer, Black *et al.* (12) found good prognosis in cases of sinus histiocytosis (SH) and follicular hyperplasia (FH). Similar findings have been obtained examining breast cancer. Paracortical hyperplasia (PH) and lymphoid reaction (LR) in T-cell regions of lymph nodes are the most favorable indicators of prognosis (13). Arguments are mixed whether or not there is a correlation between the grade of TIL and the intensity of the regional lymph node reaction (14).

Identification of TIL

Lymphocytes found in non-cancerous stomach regions are B-cells, and those seen at the cancer site are T-cells (4). The lymphocyte patterns of various tissues differ greatly depending on the presence of cancer, even in early growth stages. T lymphocytes are present in perivascular regions as well as around cancer cells, suggesting mobilization of such cells from the circulating blood (15).

TIL are most prominent in the margin of the cancer lesion. Immunoperoxidase staining using monoclonal antibodies of the OKT series (16) and Leu series (17) have been useful in determining the T lymphocyte subsets. OKT 8-positive lymphocytes, *i.e.*, cytotoxic/suppressor T lymphocytes (Tc/s), are increased in gastric cancer presenting many TIL, suggesting that OKT 8-positive T lymphocytes serve as a barrier to the development or spread of the cancer (18). Similar findings have been observed in regional lymph nodes (18). Studies with the Leu series have emphasized the importance of Leu 2-positive T lymphocytes in the TIL. This cell population also is recognized as Leu 7-positive lymphocytes.

It is uncertain at the present whether TIL activity is cytotoxic or suppressive. The availability of monoclonal antibodies which will enable a more definite distinction is awaited.

TIL Activity

TIL may exhibit cytotoxicity, natural killer activity (19) or a delayed hypersensitivity reaction (20). In some cases they may have suppressor activity (20). Such variation in the action of TIL may be related to the progression of the cancer, and is not necessarily related to the systemic immune response. Werkmeister *et al.* (21) isolated mononuclear leucocytes from colonic cancer tissue, and their immunological activity was investigated by culturing them with autologous cancer

cells. The TIL were cytotoxic to autologous cancer cells in 18 of 60 cases with large number of TIL.

Intratumoral Administration of Immunomodulators and TIL

Intratumoral administration of immunomodulators, such as Bacillus Calmette Guérin (BCG) (22), BCG-cell wall skeleton (CWS) (22), Nocardia rubra-CWS (23) and OK-432 (24), is known to increase the number of TIL. This fact suggests that survival might be increased by intratumoral administration of immunomodulators.

A study by the author and others (22) demonstrated that in patients with gastric cancer treated with immunomodulators prior to gastrectomy, TIL were more observed (70 %) than in the control group (30 %). These TIL proved to be OKT 8-positive T lymphocytes and to be Leu 7-positive, as are NK cells. In the immunomodulator-treated patients, the NK activity of lymphocytes isolated from the lesion was markedly enhanced. Additionally, a lymphoid reaction of the regional lymph nodes was present more freguently. Similar results have been obtained with intratumoral BCG-CWS in lung cancer (25).

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