Immunotherapy Combined with Chemotherapy in the Treatment of Tumors

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KEYWORDS

• Immunotherapy • Chemotherapy • Immunosuppression
• Blood-brain barrier

Chemotherapy and immunotherapy, as dual treatment modalities for cancer, have been viewed as incompatible in the past, because chemotherapy has been known to cause immunosuppression in patients. Chemotherapy may induce immunosuppression by

- Immunosuppressive cytokines
- Anergy, whereby tumor cells lose targeted antigens
- Lymphopenia
- Impaired antibody production
- Inhibition of immune effector cell function
- Reduction of major histocompatability complex expression
- Or inhibition of costimulatory proteins[1,2]

In addition, intrinsic defects in cell-mediated immunity have been found in patients harboring malignant gliomas, although purified T-cell populations have been demonstrated to respond to mitogenic stimulation.[2] Some chemotherapeutic agents at low doses have been shown to potentiate an immune response against tumor cells, however, and this has been demonstrated in a murine leukemia model.[3–5]

This article provides a broad overview of the data, including laboratory and clinical studies, currently available on the combination of immunotherapy and chemotherapy for treating cancer. The various forms of immunotherapy combined with chemotherapy include monoclonal antibodies (mAb), adoptive lymphocyte transfer, or active specific immunotherapy, such as tumor proteins, irradiated tumor cells, tumor cell lysates, dendritic cells pulsed with peptides or lysates, or tumor antigens expressed in plasmids or viral vectors. This discussion is not limited to malignant brain tumors, because many of the studies have been conducted on various cancer types, thereby providing a comprehensive perspective that may encourage further studies that combine chemotherapy and immunotherapy for treating brain tumors.

It must be noted, however, that unlike most forms of systemic cancer, the blood–brain barrier (BBB) poses a formidable challenge when attempting to devise effective treatments for tumors of the central nervous system (CNS). When treating malignant tumors of the CNS, chemotherapeutic agents must have the ability to permeate the BBB, or it can be circumvented with the use of local drug delivery mechanisms such as convection-enhanced delivery or biodegradable polymers.[6–18] Additionally, the CNS has been viewed as an immune-privileged site, and the methods utilized to elicit an immune response against many forms of systemic cancer may not have the same efficacy when treating CNS tumors. For example, it has been thought that antibodies do not permeate the BBB effectively unless an inflammatory process disrupts it. Experimental studies in animals have demonstrated that peripheral immunization can lead to the accumulation of

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antibodies in the cerebrospinal fluid and brain parenchyma at a ratio of 0.1% to 1% to the titer level found in the serum.[2] It remains debatable whether antibodies can accumulate to levels within the CNS to effectively function against pathological processes, such as tumor cells. A local delivery mechanism, such as convection-enhanced delivery, may deliver optimal amounts of antibodies to CNS tumors.

POSSIBLE MECHANISMS OF ACTION OF COMBINED CHEMOTHERAPY AND IMMUNOTHERAPY

Various mechanisms have been postulated in an attempt to explain the synergistic effects of chemotherapy and immunotherapy. Chemotherapeutic drugs may enhance the antitumor effects of immunotherapy by acting directly on the tumor and host environment, minimizing the drugs' immunosuppressive effects.[19] Some studies have demonstrated that certain drugs may modify the immunogenicity of tumor cells.[1,20–26] Some chemotherapeutic agents may cause tumor cells to become highly immunogenic, such as increasing the expression of major histocompatability complex molecules (MHC) with tumor antigens. Chemotherapy may cause tumor cell death directly with the release of a multitude of epitopes for recognition by the immune system. The induction of tumor cell death by chemotherapy may lead to phagocytosis of the dead cells by antigen-presenting cells, which may present tumor antigens to lymphocytes and incite an immune response against tumor cells, such as lysis by cytotoxic T-lymphocytes (CTLs). Moreover, chemotherapy may eliminate or reduce the activity of regulatory T-cells, in addition to its tumoricidal activity.[1,27–32] Another strategy is the causation of transient lymphopenia with chemotherapy, which may eliminate the activity of regulatory T-cells among other potential mechanisms, including the stimulation of antitumor CTLs.[33]

Administering immunotherapy may sensitize tumor cells to chemotherapy. Monoclonal antibodies may inhibit DNA repair mechanisms after DNA damage caused by chemotherapy. Also, mAbs may cause chemo-resistant tumor cells to become chemosensitive.[34–36]

The exact molecular and cellular mechanisms underlying the synergistic effects of each form of immunotherapy combined with chemotherapy have not been elucidated fully. It is also possible that the effects of each treatment modality may be independent of each other, and synergism may be contingent upon the timing and scheduling of the administration of each treatment.

LABORATORY STUDIES

Chemotherapy and mAb

Several studies have been conducted in mice to investigate the efficacy of the combination of chemotherapy and mAb against tumors.[37–43] Many of these studies administered chemotherapy and immunotherapy concurrently with some success in prolonging survival compared with either treatment modality given alone. In addition, the combination treatment was able to inhibit the growth of established tumors. Ciardiello and colleagues[42] investigated the efficacy of topotecan and an mAb against the epidermal growth factor receptor (EGFR) in a murine model of human colon carcinoma and demonstrated an enhancement in survival in the mice. The observed efficacy may have resulted from the blockade of EGFR activation and the inhibition of topoisomerase. Another study of a murine model of human breast adenocarcinoma and squamous cell carcinoma resulted in a prolongation of survival after treatment with anti-EGFR antibodies and doxorubicin, which likely led to apoptosis of tumor cells.[40] A murine mesothelioma model resulted in improvement in survival when mice were treated with anti-CD40 antibodies and gemcitabine, and a similar finding was demonstrated in a mouse model of human prostate cancer when Taxol and an mAb against herceptin were utilized.[44]

Moreover, laboratories have investigated the efficacy of immunotherapy administered before or after chemotherapy. McMillin and colleagues[45] tested the effects of trimetrexate given to mice 4 days after anti-CD137 in a murine sarcoma model. They were able to demonstrate prolongation in survival.

Chemotherapy and Active Specific Immunotherapy

Various forms of active specific immunotherapy have been combined with chemotherapy and studied in animal models.[46–56] Tumor cell lysates, tumor proteins, irradiated tumor cells, and tumor antigens expressed in viral vectors or plasmids have been utilized as modes of vaccine delivery. Many of the experimental studies involved the administration of the immunotherapy after chemotherapy, and some of them resulted in survival prolongation or inhibition of established tumors. Jeglum and colleagues[53] used a canine lymphoma model in which irradiated lymphoma cells were administered 2 weeks after vincristine and cyclophosphamide and showed an increase in survival. In a murine model of glioma, survivin RNA-transfected dendritic cells were injected subcutaneously 7 days after temozolomide was given to

the mice.[26,57] The mice lived longer when compared with mice treated with either therapy alone.

Studies also have been conducted in which active specific immunotherapy was given prior to chemotherapy. A study involving murine models of colon and lung carcinoma demonstrated inhibition of established tumor growth and prolongation in survival when the mice were treated with recombinant endoglin 7 days before cisplatin.[58] Murine models of lung carcinoma and hepatoma produced similar results when gemcitabine was administered 7 days after recombinant vascular endothelial growth factor receptor was given subcutaneously.[59] Both anti-endoglin and anti-vascular endothelial growth factor receptor antibodies in the former and latter studies, respectively, likely inhibited tumor angiogenesis. In an attempt to increase the number of tumor infiltrating lymphocytes, Hayakawa and colleagues[60] administered irradiated mouse tumor cells transduced with the costimulatory protein B7-1 4 weeks before methotrexate in a rat osteosarcoma model. The treatment resulted in inhibition of tumor growth and an increase in survival.

Chemotherapy and Adoptive Lymphocyte Immunotherapy

It has been hypothesized that the tumor microenvironment plays a vital role in the effects of the combination of chemotherapy and adoptive lymphocyte immunotherapy. In a murine model of fibrosarcoma, antigen-specific T-cells were transferred to the mice with established tumors 2 days after the administration of gemcitabine.[19] This treatment resulted in rejection of the tumors in seven out of eight mice. Pretreatment with a chemotherapeutic agent may have caused a strong release of antigens, which normally may be expressed in low levels. The increased levels of antigen likely sensitized the stromal cells for eradication by CTLs that were transferred adoptively.

CLINICAL STUDIES

Chemotherapy and mAb

Clinical trials of chemotherapy and mAb have resulted in some efficacy against cancer in patients.[61–72] A few studies have been conducted in which both treatments were administered simultaneously for pancreatic cancer, B-cell lymphoma, breast cancer, and acute myeloid leukemia (AML). In one study involving 101 AML patients, gemtuzumab was linked to calicheamicin, and complete responses, remission with incomplete platelet recovery, and no responses were observed in 13, 15, and 73 patients, respectively.[69] Bouzani and colleagues[63] administered anti-CD20 mAb, cyclophosphamide, doxorubicin, vincristine, prednisone, and methotrexate to three patients with B-cell lymphoma and observed complete responses in each of them. Two studies evaluated the effects of anti-EGFR mAb and gemcitabine in patients with pancreatic cancer. Graeven and colleagues[73] demonstrated a partial response, stable disease, and progressive disease in three, five, and four patients, respectively. The other larger study resulted in stable disease, progressive disease, and partial responses in 26, 6, and 5 patients, respectively.[74] There were no follow-up data available for four patients. In a trial of 22 patients with breast cancer, mAb specific for herceptin combined with methotrexate and cyclophosphamide were administered simultaneously.[75] Partial responses, stable disease, and progressive disease were seen in 4, 10, and 8 patients, respectively.

A larger proportion of the clinical trials involved the administration of chemotherapy after the mAb. Shin and colleagues[71] administered cisplatin 1 day after an anti-EGFR mAb in nine patients with head and neck cancer, and complete responses, partial responses, and progressive disease were observed in two, four, and three patients, respectively. In another study, 96 patients with head and neck cancer were treated with cisplatin and carboplatin 1 hour after anti-EGFR mAb.[76] Partial responses, stable disease, and progressive disease were observed in 10, 41, and 27 patients, respectively. A large study involving 202 patients with non-Hodgkin's lymphoma investigated the efficacy of anti-CD20 administered 1 day prior to cyclophosphamide, doxorubicin, vincristine, and prednisone.[64,65] Interestingly, 152 patients experienced a complete response, while 31 had progressive disease. Slamon and colleagues[77] treated a group of 235 metastatic breast cancer patients with doxorubicin, cyclophosphamide, epirubicin, and paclitaxel 7 days after an antiherceptin mAb. Progressive disease was seen in 117 patients, while partial responses and complete responses were observed in 100 and 18 patients, respectively.

Chemotherapy and Active Specific Immunotherapy

Clinical trials utilizing both chemotherapy and vaccine therapy also have been performed in patients with different cancer types, including glioblastoma multiforme (GBM), colon cancer, pancreatic cancer, prostate cancer, and small cell lung cancer.[78–85] Wheeler and colleagues[84]

investigated the clinical responsiveness of GBM to chemotherapy after vaccination. Three groups of patients were treated with chemotherapy alone (13), vaccination alone (12), or chemotherapy after vaccination (13). All patients underwent a craniotomy and received radiation. The vaccination consisted of autologous dendritic cells loaded with either peptides from cultured tumor cells or autologous tumor lysate. There were three vaccines administered 2 weeks apart, and vaccination commenced approximately 15 weeks after surgery. In the vaccine/chemotherapy and chemotherapy alone groups, temozolomide and 1,3-bis (2-chloroehthyl)-1-nitrosourea (BCNU) were administered to patients. Three patients received Gliadel wafers, which are biodegradable polymers that slowly release BCNU. The mean survival time for the chemotherapy alone, vaccine alone, and vaccine/chemotherapy groups were 16 months, 18 months, and 26 months, respectively. An analysis demonstrated a 2-year survival in 1 of 12 patients in the chemotherapy alone group, 1 of 12 patients in the vaccine alone group, and 5 of 12 patients in the vaccine/chemotherapy group. Only the vaccine/chemotherapy group had 3-year survivors; 2 out of 11 remaining patients were 3-year survivors. These results demonstrated a significantly longer postchemotherapy survival in the vaccine/chemotherapy group when compared with the vaccine and chemotherapy groups in isolation. These results are promising for the future development of vaccine trials for GBM patients.

Chemotherapy and Adoptive Lymphocyte Immunotherapy

Lymphodepletion by chemotherapy followed by the adoptive transfer of lymphocytes has been evaluated in small-scale studies in melanoma cancer patients.[86–90] In a study of 35 patients, Dudley and colleagues[89] adoptively transferred autologous cytotoxic lymphocytes with the administration of interleukin-2 1 day after cyclophosphamide and fludarabine administration. They observed a complete response in only 3 patients, partial responses in 15, and no response to the treatment in 17 patients. Larger-scale studies are needed to assess the efficacy of this treatment modality in cancer patients.

A study by Peres and colleagues[91] investigated the efficacy of high-dose chemotherapy followed by the adoptive transfer of lymphocytes in three pediatric patients with recurrent brain tumors. Two patients were diagnosed with a GBM, and the pathology revealed an ependymoma in the other patient. All three patients underwent resection of the tumors, and the tumor was used the source of antigen. The patients were treated with high-dose chemotherapy using cyclophosphamide, cisplatin, carmustine, and Taxol followed by stem cell rescue. T-cells were generated from peripheral blood after immunization with autologous cancer cells. The T-cells were expanded ex vivo and adoptively transferred to the patients. Survival was 16 months, 23 months, and 48 months, respectively. Survival in two of the patients was markedly prolonged when compared with historical controls. More studies with a larger number of patients will have to be conducted to assess the efficacy of this treatment in children with malignant brain tumors.

SUMMARY

In summary, the combination of chemotherapy and immunotherapy for treating cancer holds promise for patients suffering from this disease. Optimal treatment paradigms need to be devised to fine-tune the scheduling and timing of the administration of each treatment along with the discovery of the most effective chemotherapeutic and immunotherapeutic modalities for each type of cancer. The treatment of CNS malignancies is a more formidable task given the immune-privileged status of the CNS and the BBB. The BBB may be circumvented by local delivery mechanisms, such as convection-enhanced delivery and biodegradable polymers. Larger randomized, controlled phase 3 trials are needed to ascertain the efficacy of the combination of chemotherapy and immunotherapy.

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