

## Prospects of cancer biotherapy

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Biotherapy became recognized as the fourth modality of cancer treatment applied after surgical treatment, radiotherapy and chemotherapy since the Biological Response Modifier (BRM) theory was proposed by Dr. Oldham in the 1980s (1). Cancer biotherapy is a therapeutic method that could prohibit the growth of tumors through mobilizing the host's immune system or *via* the effect of biological agents, thereby regulating the body's biological responses (2). Biotherapy is regarded as the most vigorous and promising strategy among the cancer multimodality treatments in this century due to its advantages of high safety and effectiveness as well as low side-effects (2-4). Treatment methods of biotherapy are emerging with the development of such subjects as immunology, cell biology and molecular biology. Currently, the main approaches of biotherapy include molecule targeted therapy, gene therapy and cell therapy.

*Molecule targeted therapy:* Targeted therapy is a type of medication that aims at signature molecules over-expressed in tumor cells or unusual molecules in the tumor microenvironment. It interferes with regulation of these molecules or signal transduction pathways closely related with tumor development using selective inhibitors, thereby blocking tumor growth, progression or metastasis (5,6). Targeted drugs include small molecule compounds, monoclonal antibodies, polypeptides, *etc.* Molecule targeted therapy enhances treatment specificity and reduces drug resistance since it targets key molecules or signal transduction pathways involved in tumor development and progression (7). The targeted therapy has achieved important progress and pointed a new way forward, and is one of the most popular fields in anticancer research at present.

Since the approvals of two monoclonal antibody drugs trastuzumab (Herceptin) and rituximab (Rituxan) for treatment of metastatic breast carcinoma and diffuse large-B-cell lymphoma, respectively, in 1997, the period of history of molecule targeted therapy is less than 15 years.

Thus far, more than 10 molecule targeted drugs applied in solid tumor treatment and several such drugs employed in hematological malignancy remedies have been approved for cancer therapy (8).

Research and development of novel molecule targeted drugs is extensively carried out nowadays. Drugs with startling efficacy have continuously sprung up in the recent two years. As the survival time of patients is the gold standard for evaluating drug efficacy, the value of molecule targeted therapy has two components. On the one side, the five-year survival or cure rate of cancer patients may be raised by using the targeted drugs to reduce tumor cell differentiation or in combination with conventional surgical treatment, radiotherapy and chemotherapy. This category of drugs includes: *all-trans* retinoic acid (for acute promyelocytic leukemia), trastuzumab (for breast carcinoma), rituximab (for lymphoma) and imatinib (for gastrointestinal stromal tumors and chronic myeloid leukemia). On the other side, the targeted therapy may delay tumor progression, thus improving life quality and prolonging the lifetime of patients. Along with the advancing research, the clinical value of molecule targeted therapy will be enriched and expanded.

*Gene therapy:* Gene therapy is a biomedical technique that overcomes genetic defects or exerts therapeutic effects *via* transduction of normal or therapeutic genes into targeted cells in certain ways, thus achieving the purpose of treatment of diseases (9). The limitations of conventional cancer therapies such as surgical treatment, radiotherapy and chemotherapy have prompted searching for novel treatments. With the in-depth understanding of molecular mechanisms involving in tumor development and progression, it was realized that tumors are genopathies from the viewpoint of genetics. Correcting genetic defects may offer a new hope for cancer management.

There are two key issues that should be resolved in gene therapy. First comes the screening of the potential

genes and subsequent is the control of the safety of vectors. Based on the therapeutic strategies, the targeted genes could be proto-oncogenes or antisense nucleic acid of genes that encode tumor cell autocrine growth factors and their receptors, tumor suppressor genes, immune regulatory factor genes, anti-angiogenesis factor genes, tumor cell suicide genes, antitumor antibody genes, *etc.* According to the types of vectors, gene therapy has experienced a developing process from naked DNA, non-viral gene delivery systems, to viral gene delivery systems. Up to the present, clinical treatment schemes that use adenovirus as a gene transfer vector are most widely used in gene therapy.

The number of clinical gene therapy programs provided by the journal *J Gene Med* reached 1,537 in May 2009, in which the number of gene therapies for cancer treatment is 993, making up about 2/3 of all projects (10). However, such therapies are mainly in phase I/II clinical trials so far.

**Cell therapy:** Tumor cellular immunotherapy is a therapeutic method that utilizes biotechnologies and biological agents to separate *in vitro*, activate and reintroduce tumor specific or non-specific effector cells, either autologous or allogenic, into cancer patients (11). Compared with traditional tumor therapies, it mainly focuses on improving the status of low cellular immune function and strengthening the host's antitumor immune response.

Adoptive cellular immunotherapy could be classified into two categories based on the antigen-specificity of the infused cells: non-specific cellular immunotherapy in which the infused cells include lymphokine activated killer cells (LAK), cytokine induced killer cells (CIK) and dendritic cells (DC), and specific cellular immunotherapy in which the infused cells mainly comprise cytotoxic T cells (CTL) and helper T cells (Th).

Up to now, many clinical studies of non-specific adoptive cellular immunotherapy have been performed and achieved some prospective results (12). Sipuleucel-T (Provenge), the first therapeutic cancer vaccine, was approved to treat advanced prostate cancer by the Food and Drug Administration (FDA) on April 29, 2010. The successful development of this drug which took over 20 years opened a new era of cancer immunotherapy. In addition, several phase I/II clinical studies of adoptive cellular immunotherapy based on CIK and DC have attained preliminary results in treatment of metastatic melanoma, liver cancer, metastatic renal cancer, and gastric cancer (13-15).

Specific adoptive cellular immunotherapy based on CTL has been the focus in immunotherapy of solid tumors such as melanoma, gastric cancer, colorectal cancer and liver cancer. Several phase I studies of such therapy have been accomplished (12). However, operative treatment schemes that can be applied in the clinic for cancer treatment are rare so far because of the low inducing efficiency of CTL *in vitro*, the complicated operation, and the long period and quantity limitation of amplification that often defeat the desired results.

**Outlook:** Biotherapy will be a main direction in cancer therapy in the future. In order to further increase its therapeutic effect in cancer treatment, efforts should be directed to the following aspects. First is the development

of novel approaches of biotherapy to enhance the efficacy. Second is deeply and objectively evaluating the therapeutic effect of biotherapy through making randomized control studies in a large number of patients. Third, since biotherapy is largely adjuvant therapy and demonstrated to have a synergistic effect with conventional radiotherapy or chemotherapy, how to combine biotherapy with these traditional methods to achieve a better therapeutic effect in individualized cancer treatment should be explored in the future. Last, due to large individual differences in the efficacy of biotherapy, searching for biomarkers that could validly predict treatment outcome plays an important role in its clinical application. With the advancement of biotechnology, the means and efficacy of biotherapy will be improved constantly, which may make biotherapy occupy an increasingly important position in a comprehensive cancer treatment system.

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