Prospect of Anticancer Therapy

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Despite advances in the early detection, active treatment and focus on survivorship of cancer patients, the unfortunate reality is that many will still die of cancer. Cancer is the most common cause of death in Korea, with approximately one fourth of all deaths, 59,000, in 2001, and is increasing annually. In the past, cancer treatment focused on control of the disease, but nowadays, oncology professionals concerns are about the quality of life as well as treatments. Multidisciplinary approaches have been performed by super specialization, with remarkable advances in therapeutic modalities. Also, the continuum from cancer prevention to cancer treatment is a very important issue in this era. What treatment is best for each patient? Which methods have proven to be most effective, and how they are used to fight cancer? In general, the most common forms of treatment are surgery, radiation as both a local therapy and as chemotherapy, hormonal therapy, biological therapy, immunotherapy, antiangiogenesis therapy, and gene therapy as a systemic therapy. Conventional treatments are not adequate for the majority of cancer patients. Many patients fail to respond to conventional therapy because their tumors are remarkably resistant to chemotherapy or radiation, both of which work by damaging the DNA of the rapidly dividing tumor cells. Attempts to overcome resistance with higher doses of radiation and chemotherapeutics inevitably result in an unacceptable degree of toxicity and damage to normal tissues. But, cytotoxic therapy still remains the mainstay therapy. For the past 20 years, oncologists have been trying to assess the utility of systemic therapy in the management of solid tumors using single agent and combination chemotherapy regimens, based on the dose schedule and intensity, by the alternating or sequential use of combinations and also adjuvant and neoadjuvant therapies. In the past, most advanced cancers were usually incurable, but due to the recent molecular advances cited in the context of the field of oncology, many patients can now be offered a better chance of cure from metastatic or advanced diseases in some solid cancers, such as testicular and ovarian cancers, lymphomas and leukemia. Our ability to keep many metastatic solid tumor patients alive for much longer, while preserving a good quality of life, also represents a major advance.

In recent years, there have been substantial increases in the

numbers of new agents, with new mechanism of actions, which are thought to exert their tumor effects based on their varied pharmacological and biological characteristics. Many of these new agents have their clinical activity due to unique mechanisms of action. These mechanisms include the action of monoclonal antibodies to cell surface antigens, receptors and oncogenes, differentiating agents, immunotoxin conjugates, signal transduction inhibitors and antiangiogenic drugs. Gene transfer will also be approved for cancer therapy, and all these therapies will be guided by genomic and proteomic classifications as much as by histology or the site of origin.

Recent advances in molecular biology have documented the role of genetic alterations in tumorigenesis and have led to the development of potentially new therapeutic approaches designed to target cancer. Especially, our understanding of the molecular biological factors that influence growth control, metastasis and response to therapy has changed dramatically. Now, the point has approached where treatment strategies can be rationally designed based on relatively reliable predictive factors.

Recently, many exciting advances in the molecular mechanisms of carcinogenesis have led to the synthesis of new drugs that can inhibit tumor developed by their selective action on specific molecular targets. Signal transduction pathway inhibitors; a representative new tyrosine kinase inhibitor agent is STI 571. Clinical trials with STI 571 have dramatically demonstrated the potential of targeting molecular pathogenetic events in a malignancy. It is worth remembering that the activity of Bcr-Abl Tyrosine kinase has been clearly demonstrated as critical to the pathogenesis of chronic myelogenous leukemia (1,2). In addition to inhibiting the Abl kinase, STI 571 inhibits PDGF-R and c-kit tyrosine kinase (3). The obvious goal is to identify the pathogenetic events in each malignancy, and develop agents that specifically target these abnormalities.

The epidermal growth factor receptor (EGFR) represents a promising molecular target for exploitation in the treatment of a variety of epithelial tumors. Activation of the EGFR results in cell growth, proliferation and angiogenesis. Therefore, blockade of the EGFR can augment the antitumor activity of standard chemotherapy or radiotherapy against a variety of solid tumors (4,5). These include inhibitors of the EGFR, farnesyl transferase and of vascular endothelial growth factor (VEGF). Farnesyl transferase inhibitors inactivate the Ras protein, which is the downstream effector molecule for the ErbB receptor signalling pathway associated with radioresistance in radiotherapy (6).

Especially, squamous cell carcinoma of the head, neck and

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aerodigestive tract are particularly rich in their expression of EGFR, and the downstream signaling pathway seems to contribute directly to the growth and behavior of most kinds of malignancy. Molecular blockade of the EGFR signaling represents a promising new treatment approach in the attempt to down regulate the growth of tumors that rely on the EGFR cascade. C225 (cetuximab) is an EGFR-blocking human- chimeric monoclonal antibody, and the ZD1839 abolishing of the EGFR induced signaling, by inhibition of the receptor tyrosine kinases, improves the outcomes in patients with epithelial neoplasm (7,8), and is approved by the FDA in lung cancer. Other antibodies, such as OSI 774, and rhuMab HER2 (trastuzumab), have also been used in certain types of breast cancer patients. Angiogenesis inhibitors; vascular endothelial growth factor (VEGF) regulates the pathologic angiogenesis through enhanced endothelial cell mitogenesis, migration, remodeling of the extracellular matrix and by increasing vascular permeability. As a targeted therapy, the anti VEGF antibodies, bevacizumab and SU5416, have been shown to have independent efficacy as well as being additive with cytotoxic and radiotherapy (9). Also, TNP470 inhibits methionine aminopeptidase, which causes proliferation of vascular endothelial cells. Metalloproteinase inhibitors (MMPI); Endostatin Marimastat (BB-251), BMS-275291 and prinomastat inhibit the activation of matrix metalloproteinase (10).

Also, the development of therapies that facilitate tumor-cell apoptosis (STAT-3 inhibition), and those that combine antiangiogenic activity or cox-2 inhibition with radiation and cytotoxic agents, represented by taxanes, are valuable new directions in the treatment of epithelial malignancies. In summary, through our understanding of signaling pathways that regulate the cellular growth cell cycle and apoptosis, numerous targets for anticancer agents have emerged. The targets usually include EGFR, transmembrane protein tyrosine kinase, protein kinase C, Farnesyl transferase, angiogenesis and metalloproteinase. It has become clear, through preclinical and clinical studies, that target therapy is an important novel strategy for the treatment of cancer.

The successful development of technology for gene transfer into mammalian cells and living animals has permitted clinical applications to patients with inherited single genetic defects and to patients with cancer. Some clinical trials of gene-based therapies for cancer are as follows:

Replacement of defective tumor suppressor genes; mutations in the tumor suppressor gene, p53, have been shown to be responsible for the loss of growth regulation in many human cancers, and when wild type p53 genes are transferred to these cells, normal p53 function is restored, resulting in apoptosis of these cells (11,12). Inactivation of oncogene expression. Immunomodulatory genes; cytokine gene transfer, drug sensitization with genes for prodrug delivery and use of drug resistance genes for bone marrow protection from high dose therapy (13). Antiangiogenesis genes; Inhibitors to angiogenesis factor and basic acidic fibroblast growth factor can potentially be used to suppress cancer growth (14). Tumor targeted gene transfer; gene transfer is accomplished by viral and non-viral methods. The most commonly used vectors include the retroviral and adenoviral vectors (15). Non-viral methods include liposomes, the 'gene gun', using bombardment of cells

with gold particles and naked DNA. A review of the clinical trials of gene therapy results to date, primarily in patients with highly advanced cancers refractory to conventional treatments, indicates that these treatments can mediate tumor regression, with acceptably low toxicities (16). Vector development remains a critical area for future research. Other important areas for future research include; modification of viral vectors to reduce toxicity and immunogenicity, increase in the transduction efficiency of non viral vectors, the enhancement of vector targeting and specificity, the regulation of gene expression and the identification of synergies between gene-based agents and other cancer therapeutics. Very few complications have arisen from the gene transfer protocol, with many patients having undergone treatments on an out patient basis. Encouraging results from combined modality protocols suggest that this mode of treatment should undergo further study.

Another field of therapy, in terms of immunotherapy, focuses on T-cell mediated recognition of cancer, which is based on the preclinical findings that suggest tumor bearing animals can reject syngeneic tumors through a cellular rather than an antibody mediated mechanism.

Chemoprevention is a new approach with tremendous potential to make an impact on the control of this disease. In the future, clinical chemoprevention will require further development of clinical trials, based better molecular and mechanistic understandings of carcinogenesis. Parallel basic science and clinical research strategies must be developed for cancer prevention and treatment.

In conclusion, in the context of constant, meticulous clinical or experimental research, which has led to steady advances, the cure of a substantial proportion of patients with advanced cancer still fail. As a result, there is a need to improve the strategies of treatment for advanced diseases, and more importantly, to achieve more effective ways for the prevention and early diagnosis. In this era, where science and molecular biology rule, these approaches should especially favor gene probes and biochemical assays. New structures are needed in cancer centers that will link basic scientists, epidemiologists and oncologists in both cancer prevention and treatment research projects, especially with government driven budgets in the field of oncology.

REFERENCES

1. Savage DG, Antman KH. Imatinib mesylate-A new oral targeted therapy. *N Engl J Med* 2002;346:683-693.
2. Deininger MW, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol* 2003;21:1637-1647.
3. Druker BJ, Lydon NB. Lessons learned from the development of an abl tyrosine kinase inhibitor for chronic myelogenous leukemia *J Clin. Invest* 2000;105:3-7.
4. Herbst RS, Hong WK. Targeted therapy against the epidermal growth factor receptor *Semin Oncol* 2002;29:1-69
5. Mendelsohn J. Epidermal growth factor receptor inhibition by a monoclonal antibody as anticancer therapy. *Clin Cancer Res* 1997;3:2703-2707.
6. Cohen-Jonathan E, Muschel RJ, McKenna WG, Evans SM, Cerniglia G, Mick R, Kusewitt D, Sebt SM, Hamilton

- AD, Oliff A, Kohl N, Gibbs JB, Bernhard EJ. Farnesyltransferase inhibitors potentiate the antitumor effect of radiation on a human tumor xenograft expressing activated HRAS. *Radiat Res* 2000;154:125-132.
 7. Baselga J. New therapeutic agents targeting the epidermal growth factor receptor. *J Clin Oncol* 2000;18:54-59.
 8. Herbst Rs, Maddox AM. Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small-cell lung cancer and other solid tumors: results of a phase I trial. *J Clin Oncol* 2002; 20:3815-3825.
 9. Gorski DH, Beckett MA, Jaskowiak NT, Calvin DP, Mauceri HJ, Salloum RM, Seetharam S, Koons A, Hari DM, Kufe DW, Weichselbaum RR. Blockade of vascular endothelial growth factor stress response increase the antitumor effect of ionizing radiation. *Cancer Res* 1999;59:3374-3378.
 10. Hidalgo M, Eckhardt SG. Development of matrix metallo-protease inhibitors in cancer therapy. *J Natl Cancer Inst* 2001; 93:178-193.
 11. Harris CC, Hollstein M. Clinical implication of the p53 tumor-suppressor gene. *N Engl J Med* 1993;329:1318-1327.
 12. Takahashi T, Carbone D, Takahashi T, Nau MM, Hida T, Linnoila I, Ueda R, Minna JD. Wild-type but not mutant p53 suppresses the growth of human lung cancer cells bearing multiple genetic lesions. *Cancer Res* 1992;52:2340-2343.
 13. Deisseroth AB, Pizzorno G. The use of chemotherapy resistance in cancer treatment. *Cancer J Sci Am* 1997;3:60-69.
 14. Kong HL, Crystal RG: Gene therapy strategies for tumor anti-angiogenesis. *J Nat Cancer Inst* 1998;90:273-286.
 15. Hanania EG, Kavanagh J, Hortobagyi G, Giles RE, Champlin R, Deisseroth AB. Recent advances in the application of gene therapy to human disease. *Am J Med* 1995;99:537-552.
 16. Schiedner G, Morral N, Parks RJ, Wu Y, Koopmans SC, Langston C, Graham FL, Beaudet AL, Kochanek S. Genomic DNA transfer with a high-capacity adenovirus vector results in improved in vivo gene expression and decreased toxicity. *Nat Genet* 1998; 18:180-183.
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