Combinations in multimodality treatments and clinical outcomes during cancer (Review)

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Abstract. Combination approach could be easily considered as the future of therapeutics in all pathological states including cancer. Scientists are trying different combinations in order to determine synergism among different therapeutics which ultimately helps in the improved and more efficient management of the affected patients. Combination of multi-chemotherapeutic agents, or multi-drug therapy, may be the most commonly used strategy for cancer treatment. Monotherapy causes drug resistance and loses its response in patients after several cycles of treatment. While combining different anticancer drugs together for cancer treatment, as in the case of the cocktail therapy for HIV, not only overcomes the drug resistance but also leads to a synergistic effect, therefore showing prolonged survival for patients. The present review article is focused on different combinations in use for better efficiency of therapeutics against cancer. We searched the electronic database PubMed for pre-clinical as well as clinical controlled trials reporting diagnostic as well as therapeutic advances of various combinations in cancer. It was observed clearly that combination approach is better in various aspects including increase in efficacy, specificity and decline in the unwanted side effects.

Contents

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1. Introduction

Cancer immunotherapy is an evolving avenue in cancer therapeutics (1). It involves antigen-presenting cells (dendritic cells) that become mature after presentation of antigens and eventually migrate towards lymph nodes. This process further induces T cell and natural killer (NK) cell responses in lymphoid organs. Finally, such T cells (also B cells and NK cells) exit the lymph node, followed by entry into the tumor bed, stimulating immune response and resulting in antitumor effect (2). The immunotherapeutic agents included melanoma-differentiation antigens such as MART-1, gp100, tyrosinase or TRP-2; cancer-testes antigens such as NY-ESO-1 or MAGE-12 (3); monoclonal antibodies targeting cancer-associated proteins of Her2/neu, epidermal growth factor receptor, vascular endothelial growth factor, CD20, CD52 or CD33. Immunostimulatory monoclonal antibodies are also used, including antagonist antibodies such as anti-cytotoxic T lymphocyte antigen-4 (CTLA-4), anti-programmed death-1 (PD-1), anti-KIR and anti-transforming growth factor-β; and agonist antibodies targeting CD40, CD137, CD134 and glucocorticoid-induced TNF receptor (4). Additionally, cytokines such as interleukin (IL)-2, granulocyte-macrophage colony-stimulating factor and interferon-α are also delivered for immunotherapy (5).

Cancer vaccines used in immunotherapy are often not sufficient enough for tumor response. The rationale behind combination immunotherapy is various. One strategy is multi-immunotherapy which combines different agents to target one or more stages of the immune response, stimulating the T-cell response and overcoming the immunosuppression simultaneously. For example, it is found that T cells express multiple inhibitory receptors (6). Combining immune stimulator such as IL-15 with multiple blockades for inhibitory receptors, such as CTLA-4, PD1 and PD ligand-1, have been reported to enhance immune response (7). The trial showed a better efficacy for multimodality treatment among chemo-, radio- and immunotherapy (8).

2. Combination of hyperthermia therapy

Hyperthermia therapy, chemotherapy and/or radiotherapy are often combined together for cancer therapy. Hyperthermia is used as an efficient adjuvant treatment with radiotherapy and/or chemotherapy because it causes tumor reoxygenation.

When tumors are heated up between 39 and 43˚C, improvement in oxygenation is emerged (9). The resultant reoxygenation may last for 24 h after heating (10). It has been demonstrated that hypoxia plays a role in chemo- and radioresistance. The improvement of tumor oxygenation might increase the possibility of a positive response to radiation therapy (11). In addition, combination with hyperthermia have been reported to make tumors more sensitive towards chemotherapy as well as radiotherapy (12).

The multimodality treatment of intracavitary hyperthermia and chemoradiotherapy provided an effective and safe therapeutic modality (13). The above combination has also applied in a clinical trial involving triple-modality treatment combined full-dose radiotherapy, chemotherapy and locoregional hyperthermia therapy during advanced cervical carcinoma. After a median follow-up of 538 days, 74% of patients survived without signs of recurrence, and the overall survival rate was 84%. Long-term survival data showed that the 5-year recurrence-free survival rate was 57.5% and the 5-year overall survival was 66.1% (14,15). In another combination treatment of paclitaxel, liposomal doxorubicin and local breast hyperthermia, survival of 75% has been reported to be increased by five years (16).

Further, gemcitabine and cisplatin with regional hyperthermia also had better efficacy in advanced pancreatic cancer patients (17). The regional hyperthermia in combination with platinum-based chemotherapy was also tested on children and adolescents with recurrent or refractory germ cell tumors. It revealed that 7 of 10 patients had objective tumor response (18).

Apart from the increased chemo- or radio-sensitivity induced by heat, hyperthermia caused denaturation and aggregation of proteins to influence DNA repair and cell cycle regulation, changed the vascularity for enhanced blood flow and drug delivery, up-regulated the expression of genes to produce the family of heat shock proteins (HSPs) (19). The overexpression of HSPs turned out to be related to thermoresistance (20). Suppression the gene expression of HSPs is another kind of multimodality treatment which stimulated the T-cell immune response (21). Additionally, gold nanoparticles could be used as photothermal agents in combination with immnotherapy (22). Carbon nanotubes are agents for hyperthermia based on radiofrequency ablation or absorbance of near-infrared radiation (23).

3. Combination of anti-angiogenesis therapy

Anti-angiogenesis therapy inhibits growth of cancer by blocking the formation of new blood vessels (24). Angiogenesis is often involved in tissue regeneration and in chronic inflammatory conditions. Cancer will benefit from the new blood vessels for oxygen and nutrients, which allow cancer cells to multiply, invade nearby tissue, and metastasis (25). Angiogenesis inhibitor is a type of chemical, which interferes with the signals related to formation of new blood vessels. There are two kinds of inhibitors: Direct angiogenesis inhibitor and indirect one. Direct angiogenesis inhibitor restrains response of vascular endothelial cells to pro-angiogenic proteins; whereas indirect inhibitor blocks the synthesis of angiogenic proteins by tumor cells, reduces the activity of the proteins or blocks the expression of receptors on endothelial cells (26).

Anti-angiogenesis therapy is often combined with chemotherapy, radiotherapy or immunotherapy for additive or synergistic effect (27). By 'normalizing' tumor vessels through anti-angiogenesis therapy, it leads to decreased vascular leakage, lower intratumoral-tissue pressure and increased delivery of therapeutic agents. Due to the decreased intratumoral pressure, anti-angiogenesis therapy also increases oxygenation supply in tumor and leads to sensitivity of a tumor for ionizing radiation. The improvement in blood flow and oxygenation also leads to higher level of glucose and oxygen as well as amino acids, which will help T cells to keep activity in immunotherapy. Combining anti-angiogenesis therapy with immunotherapy enhances dendritic-cell function, decreases the number of myeloid-derive stem cells and regulatory T cells, and increase lymphocyte infiltration. In a recent study study, dendritic cell-based autologous whole tumor vaccination was utilized together with anti-angiogenesis therapy, followed by transfer of autologous vaccine-primed CD3/CD28-co-simulatied lymphocytes for recurrent ovarian cancer patients (28). In another trial, anti-angiogenesis therapy was combined with hormonal therapy on patients with hormone receptor positive breast cancer, who received first-line bevacizumab and taxane-including regimen (29).

4. Combination of photodynamic therapy

Photodynamic therapy (PDT) utilizes photosensitizing agent and a particular type of light to cure cancer. When the photosensitizing agent is accumulated in a tumor, a laser or other source of light is delivered to the areas at the same time. The photosensitizer in tumor gets activated from a ground to an excited state and release energy by returning to its ground state. The energy is then transferred to oxygen and results in generation of reactive oxygen species (ROS), which causes cellular toxicity (30). The most commonly used photosensitizer is paophyrin. Other classes of photosensitizers include chlorin, bacteriochlorin, phthalocyanine, phenothiazinium compound, porphycene, hypericin, chlorophyll derivative, texaphyrin, antracen, purpurin and hypocrellin. Among them, 5-aminolevulinic acid, methyl 5-aminolevulinate, methyl-tetrahydroxyphenyl chlorine and haematoporphyrin derivative are approved for clinical use (31).

Apart from the direct killing of cancer cells by generation of ROS, PDT also damages tumor-associated vasculature, leading to tumor hypoxia/anoxia and nutrient deficiency. It also activates immune response against tumor cells and decreases immunosuppressive effect (32). Currently, there are many clinical trials using PDT alone (33). However, most of the photodynamic-related multimodality treatments are still studied in animal models (34). There is one phase I clinical trial in which PDT was combined with surgery. The trial demonstrated the feasibility of combination with surgery and PDT (35).

5. Combination of gene therapy

Gene therapy is a novel treatment that involves the introduction of genetic material (DNA or RNA) into a person's cells to fight disease. Viral vectors have been used to deliver genes to tumor cells (36). Gene therapy could be a direct attack on

tumor cells. Delivery of tumor-suppressor genes to cancer cells and successful expression of them, or delivery of antisense oligonucleotides or rebozymes to block oncogene expression, leads to cell death or growth inhibition. Additionally, delivery of suicide genes, which are enzyme-encoding genes for metabolizing a harmless prodrug, could activate prodrugs for cytotoxicity and lead to a bystander effect. Except for the direct attack on tumor cells, gene therapy also stimulates one's immune response, target to prevent angiogenesis, or overcome the cell resistance and make cancer cells more sensitive to other therapies, such as chemotherapy and radiotherapy (37). Theoretically, gene therapy has the ability to combine with all the above therapies including chemotherapy, immunotherapy, hyperthermia therapy, anti-angiogenesis therapy and PDT by targeting certain pathways of cancer cells and promote the efficacy of other therapies. Recent cutting edge research is concerned with RNA interference (RNAi) therapy involving microRNA and small interfering RNA (38). It shows the potential of anticancer effect through inhibiting over-expressed oncogenes, blocking cell division and promoting apoptosis. It also suppresses therapeutic resistance to enhance other therapies (39).

Currently, there are many clinical trials for gene therapy alone without combination with other therapies (40). Many combination gene therapies are still studied at preclinical level. RNAi gene therapy has come to clinical trials but not combined with other therapy modalities. One example of combination gene therapy was conducted on prostate cancer patients with herpes simplex virus-thymidine kinase (41).

6. Conclusion

It can be concluded from the above that the combination approach is crucial in enhancing the efficacy of cancer therapeutics in variable therapeutic approaches.

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