Gene-directed enzyme prodrug therapy (GDEPT) is a suicide gene therapy approach where the delivered gene encodes an enzyme that activates a prodrug administered systemically. The prodrug is non-toxic per se but begets an active metabolite due to action of the expressed enzyme. As an anticancer strategy, GDEPT couples chemotherapy with gene therapy and offers immense therapeutic potential with more tumor specificity and less systemic toxicity. Another additional benefit of such an approach is the bystander effect by which the active cytotox metabolite diffuses into neighboring, non-transfected tumor cells and kills/radiosensitizes them.

Most solid tumors have a hypoxic population of cells that are both chemo and radio-resistant. Such a hypoxic microenvironment of the tumor can be exploited therapeutically by using the bioreductive prodrug in the GDEPT approach where the gene expresses the prodrug-activating enzyme preferentially in hypoxic cells of solid tumors. One prominent example of bioreductive prodrug is tirapazamine (TPZ or SR 4233). Chemically, tirapazamine is 1, 2, 4-benzotriazin-3-amine 1, 4-dioxide, which becomes activated by NADPH:cytochrome 450 reductase (P450R), to give cytotoxic metabolites, mainly its 1-N-oxide (SR 4317). Both, generating free radicals and oxidizing these radicals to cause DNA strand breaks have been suggested as the possible mechanism of action of TPZ.

The hypoxia-regulated GDEPT using TPZ exploits the anaerobic activation of hypoxia inducible factor (HIF-1) - a transcription factor that binds to hypoxia response element (HRE) of genes encoding proteins (e.g. GLUT-1, VEGF and enzymes of anaerobic glycolytic pathway) that help tissues cope with hypoxia in various ways. To bio-activate TPZ, the expression of P450R is placed under the transcriptional control of HIF-1 through the use of hypoxia response element (HRE) in the expression cassette. The gene construct is finally delivered to the target tissues mainly via adenovirus.

Preclinical studies of TPZ have demonstrated its ability to potentiate the antitumor effect of radiotherapy and chemo-therapy significantly, in particular, platinum-based drugs (e.g. cisplatin) and taxanes, in both murine and human xenograft models. This encouraging data has initiated Phase I, II, and III trials with TPZ in combination with cisplatin for the treatment of solid tumors including non-small cell lung cancer, breast cancer, head and neck cancer, and melanoma and as an adjuvant to radiotherapy in Phase II trials for head and neck cancer, cervical cancer and glioblastoma multiforme.

Phase III trials using cisplatin and TPZ for the treatment of advanced non-small cell lung cancer demonstrated a significant survival benefit for patients treated with the combined regimen showing a doubling in response rate compared with patients treated with cisplatin alone. A partial beneficial response of TPZ/P450R has also been found in breast carcinoma in Phase I clinical trial. Recently, the Stratford group at the University of Manchester has found complete tumor regression using TPZ in a human tumor model (HT 1080 fibrosarcoma) transfected with adenoviral construct containing P450R gene. Thus hypoxia-regulated GDEPT using tirapazamine provides an optimistic, tempting approach for treating solid malignant tumor with more specificity and less toxicity in future.

Sources

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