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Angiogenesis, thymidine phosphorylase, and resistance of squamous cell head and neck cancer to cytotoxic and radiation therapy.

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Source

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Abstract

Thymidine phosphorylase (TP), an enzyme involved in the thymidine synthesis and degradation, has been shown to promote tumor angiogenesis. Both TP expression and tumor vascularization are putative postoperative prognostic markers of cancer. Because of its bifunctional role, TP may have interactions with cytotoxic drugs or radiation via pathways requiring thymidine or prodrug activation. The microvessel score and TP expression were examined immunohistochemically on paraffin-embedded bioptical material from 94 locally advanced squamous cell head and neck carcinomas. All patients were treated with conventionally fractionated radiotherapy combined with induction (platinum- and 5-fluorouracil-based) or concurrent platinum chemotherapy. The follow-up of patients ranged from 6 to 108 months (median, 48 months). Nuclear TP expression was significantly associated with increased microvessel score ($P < 0.0001$, $r = 0.45$). A low percentage of cancer cells with nuclear TP expression in pretreatment biopsies was associated with a high rate of CR after combined chemoradiotherapy ($P = 0.006$) and induction chemotherapy (0.01). A better local relapse-free and overall survival was also observed in these patients ($P = 0.001$ and $P = 0.0005$, respectively). Biospies on the day after the delivery of 20 Gy of conventionally fractionated radiotherapy showed residual cancer cell nests, frequently of high vascularization and of intense nuclear TP reactivity. It is concluded that thymidine phosphorylase is associated with angiogenesis, with resistance to radiotherapy and cytotoxic therapy, and with poorer survival in squamous cell head and neck cancer. A strong rationale is provided for subsequent clinical trials of concurrent radiotherapy and chemotherapy with antiangiogenic agents or with specific TP inhibitors.