심포지움 9

Palliative Chemoetherapy for Advanced Head and Neck Cancer

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Chemotherapy may be administered to palliate symptom in patients with incurable head and neck cancer or as an adjuvant to radiation therapy or surgery or both to improve the probability of cure.

Patients with recurrent squamous cell carcinoma of the head and neck (SCCHN) have a 6-month median survival and a 1-year survival rate of approximately 20%. Chemotherapy may be achieve tumor regression and palliate symptoms caused by the cancer. The response rate to various chemotherapeutic agents are reasonably well defined; whether tumor regression translates into meaningful palliation when weighed against the toxicity of treament is less clear.

Approximately response rate to single chemotherapeutic agents are as follows: methotrexate, 31%; bleomycin, 21%; cisplatin, 28%; fluorouracil, 15%; ifosfamide, 23%; paclitaxel, 15% to 40%; docetaxel, 30%; vinorelbine, 18%; gemcitabine, 13%. Single-agent chemotherapy is often used for patients with relatively marginal performance status and who are unwilling to accept the additional toxicity fo combination chemotherapy.

The gold standard combination chemotherapeutic regimen is cisplatin 60 to 100mg/m^2 on day 1 and fluorouracil 1000 mg/m^2 daily for 96-hour infusion, administered every 3 to 4 weeks. The average response rate is approximately 50% with about 16% complete response. The combination of paclitaxel or docetaxel with either cisplatin or carboplatin results in response rate of 30% to 40% with complete responses observed in about 10%. The median duration of response is approximately 4 months and median survival remains approximately 6 months. The toxicities of the taxane-based regimens are probably similar to those of the older drug combinations.

Recently, targeted therapies have been explored in attempts to improve on the poor outcomes in incurable SCCHN. Since the first description of the epidermal growth factor receptor (EGFR) in 1980, interest has grown in targeting this protein in cancer therapy. Expression of EGFR has been linked to carcinogenesis, metastasis, and survival in SCCHN patients. Indeed, EGFR expression has been found to relate closely to prognosis in head and neck cancer, higher levels correlating with poorer progression-free and overall survival. phsphorylation of EGFR cytoplasmic tyrosine residues initiates a cascade of signals that includes activation of the mitogen-activated protein kinase pathway. The mitogen-activated protein kinase pathway culminates in activation of nuclear translocation of the extracllular signal-regulated kinase 1 and 2 and transcription of its target genes. Preclinical studies have confirmed that interruption of EGFR phosphorylation can inhibit these downstream activation events, lead to cell cycle arrest, and compromise tumor growth.

ZD1839 (gefitinib) is an oral, low-molecular-weight anilinoquinazoline that reversibly inhibits EGFR tyrosine kinase activity. It has demonstrated an acceptable toxicity profile in phase I trials with predictable pharmacokinetics that established dose, schedule, and dose-limiting toxicity. In the recent study, patients with recurrent or metastatic SCCHN were treated with single-agent ZD1839 500mg/d. Fifty-two patients were enrolled with a median age of 59 years. ZD1839 has Single-agent activity with response rate of 10.6% and a disease control rate of 53%. Median time to progression and survival were 3.4 and 8.1 months, respectively.

Other EGFR inhibitor trials in SCCHN have shown remarkably similar results. Cetuximab, a monoclonal antibody directed at the EGFR, yielded response rates of 11% when combined with platinum therapy in two separate phase II trials in platinum-refractory patients and 23% when combined

with cisplatin as first-line therapy. Another small-molecule TKI, OSI-774, given to patients similar to those in SCCHN produced a response rate of 6%.

One strategy to enhance the efficacy of anti-EGFR therapy while maintaining tolerability is to add in another targeted therapy with nonoverlapping toxicity. As with EGFR, cyclo-oxygenase-2(COX-2) is overexpressed in SCCHN, and its expression correlated with poor prognosis. COX-2 is an inducible enzyme that results in an array of downstream events, including suppression of apoptosis and activation of proliferation and angiogenesis. Crosstalk between EGFR and COX-2 has also been demonstrated at the level of activation. The potential for enhanced activity of combining EGFR and COX-2 blockade has been confirmed in preclinical combination studies of EGFR TKIs and COX-2 inhibitors.

Last year, phase I study has been reported to establish the appropriate dosing and safety profile of gefitinib plus the COX-2 inhibitor, celecoxib, in subjects with incurable SCCHN. Nineteen patients with unresectable recurrent locoregional and/or distant metastatic SCCHN with progressive disease after at least on prior chemothrapy or chemoradiotherapy regimen were enrolled onto this study. In this study, no dose-limiting toxicities were encountered at any dose level. The most common toxicities were acneiform rash, diarrhea, hand reaction, dyspepsia, and anemia. Four of 18 patients assessable for response(22%; 95CI, 2% to 42%) achieved a confirmed partial response.

Salivary gland cancers are uncommon malignancies and account for 7% of head and neck tumors. Among the many different histologic subtypes of salivary gland cancers with heterogeneous clinical behaviors, adenoid cystic carcinoma (ACC), lymphoepithelioma-like salivary gland carcinoma, and myoepithelial salivary gland carcinoma share the common feature of c-kit overexpression, rendering these subtypes attractive for molecular targeted therapeutics. Approximately 22% of malignant salivary tumors are ACC, with a greater occurrence in minor than major salivary glands. The natural history of ACC is often protracted, with patients occasionally living for 10 to 20 years after confirmation of metastatic disease. Typical survival figures are 50% to 90% at 5 years, 30% to 67% at 10 years, and 25% at 15 years, respectively.

Initial definitive therapy for these malignancies usually consists of surgical resection followed by radiotherapy for tumors deemed to have a high risk of local recurrence. The role of systemic therapy in ACC is in the management of local recurrence no longer amenable to additional surgery or radiotherapy. The response rates of ACC to conventional cytotoxic chemotherapy have been generally modest, and were primarily derived from small institutional series and clinical trials. For example, the objective response rates of ACC to cytotoxic agents such as fluorouracil, anthracyclines, platinum compounds, paclitaxel, and vinorelbine are in the range of 15% to 30%. Duration of responses to chemotherapy typically was in the range of 6 to 9 months, with some responses lasting in excess of a year.

The c-kit proto-oncogene encodes a transmembrane cell surface receptor in the same subclass the receptor for platelet-derived growth factor and colony-stimulating factor. C-kit expression was identified in ACC(20 of 25), and lymphepithelium-like(6 of 6) and myoepithelal(2 or 2) carcinomas of the salivary gland. C-kit overexpression is likely implicated in the pathogenesis of these salivary gland tumors, but genetic mutation is not the mechanism of c-kit activation. Kit-positivity was associated with histologic grade 3 tumors and solid growth pattern.

Imatinib is a protein tyrosine kinase inhibitor. It has been shown to inhibit potently the tyrosine kinases of ABL, the platelet-derived growth factor receptor(PDGFR), and the receptor for c-kit. Imatinib has also been evaluated in a number of other tumors expressing c-kit or PDGFR, such as GISTs, small-cell lung cancer, and systemic mast cell disease with varying levels of efficacy. Recently a multi-institutional phase II study to evaluate the safety and efficacy of single-sgent imatinib in ACC. But because of the lack of activity, the study has been stopped after the first stage and additional evaluation of imatinib in this population is not warrented. Overexpression of wild-type c-kit was not sufficient for clinical benefit from imatinib in ACC. Nevertheless Faivre et al stated that on objective response has been seen on their study, and that at least two other responses have been observed by others and published as a case report.

Considering the few possible alternatives given to patients with recurrent or metastatic progressive ACC, we consider that, although sporadic, evidence of antitumor activity deserves further clinical investigation.

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