Future Directions in the Treatment of Squamous Cell Carcinoma of the Head and Neck: The Role of UFT

Review Article [1] | September 02, 1997
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Squamous cell carcinoma of the head and neck is a potentially curable neoplasm. Historically, the standard approach to treatment has been either surgery or radiation therapy, or a combination of the two. Over the past

Introduction

Squamous cell carcinoma of the head and neck is a potentially curable neoplasm if it is detected while restricted to the head and neck. Stage I and II neoplasms are often curable with either radiation or surgery as the sole modality of treatment. Stage III and IV disease, however, recurs in the majority of patients despite aggressive initial management with surgery and/or radiation therapy. If the disease recurs in the head and neck region, salvage may be attempted with additional surgery or radiation, but the long-term survival after salvage is only about 20%. Metastatic recurrence of disease is not curable, except in the rare case of isolated metastatic disease managed with surgical metastasectomy. In general, therefore, patients with recurrent unresectable local disease or metastatic disease are treated without curative intent.

Chemotherapy

The role of chemotherapy in the treatment of squamous cell carcinoma of the head and neck has been evolving, with chemotherapy now playing an important role in palliative management of patients with either locally advanced or metastatic disease. The drugs used traditionally in the management of squamous cell carcinoma of the head and neck include cisplatin (Platinol), carboplatin (Paraplatin), 5-fluorouracil (5-FU), methotrexate, and bleomycin (Blenoxane).[1-6] More recently, the taxanes (docetaxel [Taxotere], paclitaxel [Taxol]) have been evaluated for their efficacy in squamous cell carcinoma of the head and neck.[7-9] Additionally, tegafur and uracil in a 1:4 molar ratio (UFT), available for years in Japan for the treatment of squamous cell carcinoma of the head and neck, is now being explored in the United States, Canada, and Europe for potential use in the management of squamous cell carcinoma of the head and neck and other malignancies.

When used individually as palliative therapy, these drugs produce overall response rates of only 15% to 40% and response durations are brief, usually less than 6 months.[8-11] Because of the low rate of response to single-agent chemotherapy, many clinical trials have concentrated on combination regimens. While response rates have been shown to be improved, studies to date have failed to reproducibly demonstrate an improvement in response duration or median survival when combination regimens are compared to standard surgery and radiation therapy.[1,12-15] On the other hand, aggressive (high dose) combination chemo-therapy for palliation has doubled the 1-year survival rate from 20% to 40%. This progress comes at a significant cost in terms of increased toxicity, hospitalization, and restricted patient eligibility.[16,17]

Combination Regimens for Induction Therapy

Beginning in the 1970s, combination chemotherapy has been studied in the induction setting in potentially curable patients with squamous cell carcinoma of the head and neck. Initial studies using combination platinum and 5-FU demonstrated that complete remission rates exceeding 50% were achievable.[4] Additionally, studies demonstrated a benefit of cisplatin over carboplatin and of infusional 5-FU over bolus 5-FU.[1,14] Further, refinement of this combination involved the addition of leucovorin as a stabilizer of the 5-fluorodeoxyuridine-1-phosphate (F-DUMP)/thymidylate synthase complex and yielded even higher overall response rates. [6,12,18,19] A recent report of an induction regimen utilizing a combination of docetaxel, 5-FU, cisplatin, and leucovorin demonstrated that pathologic response rates approaching 100% were achievable at the primary site in squamous cell carcinoma of the head and neck.[20]
Most trials using an induction regimen based on cisplatin and 5-FU have included definitive radiation therapy as an integral part of the curative treatment regimen. It is clear that patients who respond to chemotherapy have an excellent prognosis following definitive radiation therapy. Some investigators, however, attribute this chemotherapeutic response to the antineoplastic activity of the induction chemotherapy, while others view it merely as a predictor of tumor radiosensitivity. While it has been demonstrated in a randomized setting that both induction chemotherapy followed by radiation therapy, and combined chemotherapy plus once-daily radiation therapy are superior in terms of overall survival to once daily radiation alone in the setting of unresectable locally advanced squamous cell carcinoma of the head and neck,[21,22] similar data are not available for potentially resectable disease.[23] Of interest, a small but significant group of patients with locally advanced disease can be cured with induction chemotherapy alone, but at present there is no reliable way to identify these patients.[24] Results of hyperfractionation-radiation programs have suggested increased response rates relative to daily radiation programs, but the roles of hyperfractionated or accelerated radiation used with induction therapy, or concomitant chemotherapy/hyperfractionated radiation regimens, are just beginning to be explored and should be regarded as investigational.[25]

**Stage III and IV Disease** in nonmetastatic stages III and IV squamous cell carcinoma of the head and neck, the traditional approach to curative management has included surgery and radiation therapy, with typical long-term survival rates in the range of 20% to 40%. Unfortunately, many patients who undergo curative resection are left with major, permanent functional deficits, including loss of speech and severely impaired swallowing capability. The United States Veteran’s Administration trial in 1991 and, more recently, a trial by the European Organization for the Research and Treatment of Cancer have shown in a randomized setting that induction therapy with Platinol 100 mg/m² and infusional 5-FU (PF) 1,000 mg/m²× 5 d followed by definitive once-daily radiation therapy can preserve organ function in two thirds of surviving patients with locally advanced laryngeal cancer, without compromising overall survival in comparison with patients treated with surgery and adjuvant radiation therapy.[26,27] Overall survival in this setting, however, is still only on the order of one in three patients.

A number of currently active studies have been designed with the goal of improving on the results of the Veteran’s Administration and European Organization for the Research and Treatment of Cancer experience. As mentioned, several studies have attempted modulation of the effect of 5-FU using leucovorin, and, although multiple phase II studies have documented an increase in response rates, there are no convincing data to suggest that these leucovorin-containing regimens extend survival. As a result, explorations of alternative fluorinated pyridine analogues such as tegafur, which has been in use in Japan for a number of years, are beginning in Europe and the United States in patients with squamous cell carcinoma of the head and neck. Tegafur, also known as Ftorafur, is effectively a 5-FU prodrug converted into 5-FU by hepatic cytochrome P-450 enzymes.[28-30] In comparison with 5-FU, tegafur has the added advantage of reliable absorption in the small intestine and thus it can be administered orally. Studies also have shown that when tegafur is administered concomitantly with uracil, there is an enhanced tumor-to-plasma concentration ratio for FdUMP, the active metabolite of tegafur. The mechanism for this enhancement appears to be uracil-mediated inhibition of the 5-FU degradative enzyme dihydouracil dehydrogenase in tumor tissue, without significant inhibition of FdUMP binding to thymidylate synthetase. This effect of uracil on intratumor tegafur metabolism is thought to result from the different binding constants of the uracil and FdUMP moieties with respect to dihydouracil dehydrogenase and thymidylate synthetase.[31]

A 1:4 molar ratio of tegafur to uracil has been found to result in the highest tumor-to-plasma concentration and the highest tumor kill in experimental systems.[32] Based on these observations, uracil and tegafur have been combined at this ratio for a formulation known as UFT, which has been in clinical use in Japan for many years. Combined phase II data suggest that it is an active antineoplastic agent with an activity spectrum similar to that of 5-FU.[33] Of interest, UFT activity in Japanese patients with squamous cell carcinoma of the head and neck has been reported in the range of 24% to 30%.[34,35]

**UFT in Treatment**

The Spanish experience with UFT as part of induction therapy for patients with squamous cell carcinoma of the head and neck is equally promising. Valverde and colleagues have reported their results of a randomized trial of induction chemotherapy with Platinol plus UFT (PU) vs PF, followed by
definitive daily radiation therapy, as potentially curative treatment of squamous cell carcinoma of
the head and neck. In this study, 67 patients with squamous cell carcinoma of the head and neck
were randomized to receive either cisplatin 100 mg/m$^2$/d followed by a continuous infusion of 5-FU
1,000 mg/m$^2$/d for 5 days or the same dose of cisplatin followed by UFT 300 mg/m$^2$/d in divided
doses orally for 20 days. Four cycles of each therapy were administered before daily radiation
therapy to a total dose of 50 to 70 Gy. Response rates in the two arms were similar: In the PU arm
the complete response (CR) rate was 18% and the partial response (PR) rate was 60%.
Corresponding figures in the PF group were 20% CR and 52% PR. Toxicities also were comparable
between the two arms. At the completion of radiation therapy, CR rates were 50% for the PF arm and
49% for the PU arm. With a median follow-up of 84 months, the investigators report a disease-free
survival of 29% for the PF arm and 27% for the PU arm.[365,37]

US Trials

UFT has not yet been approved for use in the United States, but, thanks to collaborative efforts
of the Bristol-Myers Squibb Pharmaceutical Company, Taiho Pharmaceutical Co., Ltd., and multiple
clinical investigators in the United States, many trials are under way. The majority of these trials are
focusing on neoplasms of the gastrointestinal system, but investigators at Dana-Farber/Partners
Cancer Care are studying the activity and toxicity of combination UFT/leucovorin in patients with
advanced squamous cell carcinoma of the head and neck.
The rationale for combining UFT with leucovorin is similar to that for combining 5-FU with leucovorin.
As noted, the addition of leucovorin to PF in induction regimens for squamous cell carcinoma of the
head and neck significantly enhances the antitumor activity of PF, albeit with a substantial increase
in toxicity. Because the pharmacology of UFT differs somewhat from that of infusional 5-FU, it is
possible that combination UFT/leucovorin may preserve the antitumor efficacy of the 5-FU/leucovorin
combination, without the associated neutropenia and mucositis. Anecdotally, this seems to be the
case in the hands of Japanese investigators.[38]
Additionally, because UFT/leucovorin is an oral regimen, the need for hospitalization and prolonged
infusion could be eliminated for patients undergoing potentially curative or palliative treatment,
resulting in reduced medical expenses and an enhanced quality of life during treatment for
squamous cell carcinoma of the head and neck.
With this background, a phase II trial of UFT plus leucovorin in advanced regional or metastatic
squamous cell carcinoma of the head and neck was opened to accrual at the Dana-Farber Cancer
Institute in late 1996. Patients are eligible for this trial if they have had neither palliative nor
induction chemotherapy in the 6 months preceding enrollment. Patients will receive UFT 300
mg/m$^2$/d (rounded to the nearest 100 mg) plus leucovorin 90mg/day, both given orally in three
divided daily doses. Treatment will be for 28 consecutive days, followed by 1 week without treatment
before reinitiating therapy. The study end points are tumor response rate and toxicity. To date, two
patients have been enrolled. One patient has achieved a PR following completion of one cycle of
therapy, with minimal toxicity.

Conclusion

The ultimate place of UFT in the armamentarium of weapons against head and neck cancer is still
uncertain. However, given the previous Japanese experience and the ongoing trials in the United
States and elsewhere, a possible role for UFT should certainly be defined before the new
millennium.

References:
1. Forastiere A, Metch B, Schuller D, et al: Randomized comparison of cisplatin plus fluorouracil and
carboplatin plus fluorouracil vs methotrexate in advanced squamous cell carcinoma of the head and
for patients with advanced squamous cell carcinoma of the head and neck. Cancer Treat Rep
3. DeConti R, Schoenfeld D: A randomized prospective comparison of intermittent methotrexate,
methotrexate with leucovorin, and a methotrexate combination in head and neck cancer. Cancer


20. Colevas A, Norris C, Busse P, et al: Taxotere(docetaxel), cisplatin (CDDP), 5-fluorouracil (5-FU) and leucovorin (LV) (TPFL) induction chemotherapy for locally advanced squamous cell carcinoma of


37. Gonzalez-Larriba J: Neoadjuvant chemotherapy with cisplatin plus 5-FU versus cisplatin plus UFT

38. Taguchi T: Japanese experience with UFT. Oncology 11(9) [supp 10]):30-34, 1997.

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