REVIEW ARTICLE

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Oral Chemotherapy in Head and Neck Cancer

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Abstract

Chemotherapy plays an important role in the palliative treatment of head and neck cancer and in the neoadjuvant setting for larynx preservation. Together with concomitant radiotherapy, chemotherapy is also important for the curative and palliative therapy of unresectable head and neck cancer. Although issues relating to anatomical and pharmacological constraints exist, new orally administered drugs, as well as oral substitutes for the currently utilised intravenous drugs, would be extremely desirable in each of these situations. Of the oral fluorinated pyrimidines, tegafur/uracil (UFT®) alone produced a complete response rate of 19%, and combination therapy of tegafur/uracil or tegafur with cisplatin or carboplatin has produced response rates comparable to those seen with intravenous fluorouracil (5-FU) plus cisplatin or carboplatin. An initial dose-finding study of 5-FU plus eniluracil indicates that further studies are warranted. The ribonuclease reductase inhibitor hydroxycarbamide (hydroxyurea) has been extensively studied in combination with 5-FU and radiotherapy (the FHX regimen) in patients with head and neck cancer, with high rates of local control. Improvement in locoregional and distant control rates may occur when FHX is combined with additional systemically active agents (cisplatin then paclitaxel) and hyperfractionated radiotherapy is used. Good candidate drugs for head and neck cancer include BMS-182751, an oral platinum complex, and capecitabine and S-1, other oral fluoropyrimidines. In addition, methotrexate and cyclophosphamide both have some activity in head and neck cancer and deserve further investigation.

It is estimated that in 1998 there will be 41 400 cases of head and neck cancer (HNC) in the US alone, and that approximately 12 300 people will die of this disease.[1] This problem is of even greater magnitude in many other countries. The majority of patients with early-stage disease will be cured with local modalities of surgery or radiotherapy (RT) alone and will not require chemotherapy. Approximately 60% of all patients with HNC will present with either locoregionally advanced (stage III or IV) disease or will develop locoregional recurrence or metastases. These patients may require chemotherapy as part of a curative multimodality treatment regimen or for palliation of incurable recurrent or metastatic disease.

Chemotherapy plays a diverse role in HNC, with some uses considered as acceptable standard treatment options while others remain under active clinical investigation. For patients with incurable locoregional recurrences or metastases, chemotherapy plays a palliative role. At least 1 in 3 patients can derive tumour shrinkage and a meaningful

benefit from chemotherapy. The role of chemotherapy in this setting is palliative, however, as few studies have shown that it provides more than minimal prolongation of life. Systemically active drugs for HNC include cisplatin and carboplatin, fluorouracil (5-FU), methotrexate, bleomycin, and the taxanes, paclitaxel and docetaxel. Two large, randomised trials have established that multi-agent chemotherapy is more active than single agent chemotherapy alone. The combination of cisplatin and 5-FU in these trials showed a response rate of 32%.[2,3] Even though this exceeded the response rate of single agent cisplatin, 5-FU, or methotrexate, survival was not improved.

Chemotherapy has an additional role as part of multimodality treatment of locoregionally advanced HNC. Administration of 2 or 3 cycles of neoadjuvant cisplatin and 5-FU can allow for larynx preservation in a majority of patients with laryngeal or hypopharyngeal cancer.[4,5] Cisplatin given concomitantly with RT, followed by adjuvant cisplatin and 5-FU, improves survival for patients with nasopharyngeal cancer compared with RT alone.[6] Additionally, meta-analysis of a large number of randomised trials has shown that single agent or combination chemotherapy, given to patients concomitantly or alternating with RT, can improve survival compared with RT alone.[7,8] Other uses of chemotherapy remain promising but investigational.

On the basis of the known systemic activity of intravenous drugs, several oral drugs have been used in the treatment of HNC (table I) and others are under clinical investigation. This paper reviews the data on the use of oral chemotherapy drugs for HNC.

Table I. Oral chemotherapy drugs in use or under investigation for head and neck cancer[a]

Previously studied drugs
Tegafur/uracil (UFT®)
Etoposide
Hydroxycarbamide (hydroxyurea)
Oral fluorouracil/eniluracil
Methotrexate
Other candidate drugs not studied
BMS-182751
Capecitabine
S-1
Cyclophosphamide

a A number of drugs have undergone clinical trials in head and neck cancer. Listed above are these drugs, as well as several others which are appropriate candidates for clinical trials in head and neck cancer.

1. Special Issues in HNC Patients

Special attention needs to be paid to the potential impediments in the bioavailability, pharmacokinetics, and drug access in patients with HNC. These issues are more thoroughly described in several other articles in this supplement.[9,10]

Oral administration of chemotherapy may be difficult in HNC patients who have swallowing dysfunction related either to their tumour or its treatment.[11] Large, untreated tumours of the oral cavity and oropharynx may cause dysphagia or odynophagia. Some patients may aspirate and thus for safety reasons are unable to take pills orally. Patients on treatment may develop xerostomia and mucositis, which at times may be severe enough to prevent the swallowing of pills. Many of these patients will have a gastric or jejunal feeding tube. Even though oral drugs can be crushed or solubilised to pass through these tubes, some variability may occur in both the administered dose and the absorption of the drug. Other factors may lead to alterations in the bioavailability and pharmacokinetics of oral chemotherapy. In particular, hepatic dysfunction, although difficult to measure, is common in these patients, many of whom have a prior history of alcohol abuse. Additionally, low serum albumin levels resulting from liver failure or malnutrition may interfere with proper transport of some chemotherapy drugs. Finally, many patients with HNC suffer from polysubstance addiction and/or poverty, which can make the cost of the drugs or compliance with the schedule a problem.[11]

2. Oral Chemotherapy Drugs

2.1 Fluorinated Pyrimidines

2.1.1 Tegafur/Uracil, Tegafur

Tegafur/uracil (UFT®) is a 4 : 1 molar mixture of uracil and tegafur (ftorafur). The development

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of this drug has generally taken place in Japan and Spain. Tegafur (1-[2-tetrahydrofuryl]-5-fluorouracil) is gradually converted to 5-FU by the hepatic cytochrome P-450 enzymes. Uracil competitively inhibits the catabolism of 5-FU via dihydrouracil dehydrogenase without inhibiting the anabolic (active) pathways. As a result, there is a constant supply of 5-FU and its active metabolites, with minimal buildup of the inactive and potentially toxic metabolites of 5-FU. In phase I studies, the maximal tolerated dose for long term administration of tegafur/uracil was found to be 600 mg/day, given in 2 to 3 divided doses. Gastrointestinal toxicity was the dose-limiting toxicity, and included an 11% incidence of diarrhoea and a 5% incidence of stomatitis. Also noted was a high tumour-to-normal ratio of tegafur/uracil tissue concentrations.[12]

In a phase II study of tegafur/uracil as a single agent for previously treated HNC, a total of 43 patients were treated continuously at a dose of 600 mg/day. The complete response (CR) rate was 19% and the partial response rate was 19%.[13]

Tegafur/uracil and its tegafur component have been extensively studied in combination with cisplatin and carboplatin by the Oncopaz Group in Spain. The results of these studies in patients with previously untreated, locoregionally advanced HNC are shown in table II. In 3 studies of cisplatin or carboplatin in combination with tegafur [with calcium folinate (leucovorin) in one study], the CR rate in the neoadjuvant setting was 22 to 33%. The overall response rate was 59 to 94%. This is approximately equal to what would be expected with cisplatin and infusional 5-FU.[14,15] In fact, one small, randomised study compared cisplatin and infusional 5-FU to cisplatin and continuous oral tegafur/uracil. The complete and overall response rates in the 67 randomised patients were identical in the 2 arms (table II).[16] There was slightly less toxicity with the tegafur/uracil regimen, and inpatient hospitalisation was not needed in the tegafur/uracil group.

One study examined tegafur/uracil as a radiosensitiser.[17] In this report, 52 laryngeal cancer patients treated with tegafur/uracil and RT were compared with 113 historical controls treated with RT alone. This study (reported in English in abstract form only) showed a significant improvement in disease-free survival and overall survival for the group treated concomitantly with tegafur/uracil. Tegafur/uracil remains an attractive drug for the treatment of HNC, and more studies directly comparing tegafur/uracil with infusional 5-FU are needed. Approval of tegafur/uracil in the US is still pending.

2.1.2 Oral 5-FU With Eniluracil

The efficacy of combination of oral 5-FU and eniluracil (GW-776C85, ethynyluracil) as treatment for several diseases, including colorectal cancer, breast cancer, and HNC, is under active investigation. The bioavailability of oral 5-FU is erratic, leading to wide variability in serum 5-FU concentrations. Eniluracil is an oral dihydropyrimidine dehydrogenase (DPD) inhibitor. Oral administration of this drug causes near-complete inhibition of DPD, and therefore allows for more consistent bioavailability of oral 5-FU.[18] Preliminary results of a trial of oral 5-FU, eniluracil, and concomitant RT in patients with HNC have been published in abstract form.[19] In this study, 13 poor-prognosis HNC patients received oral 5-FU (2.5 to 7.5 mg/m^2

Table II. Studies of tegafur/uracil or tegafur-based combinations in previously untreated patients with head and neck cancer

Reference	No. of patients	Drugs	CR (%)	OR (%)
Gonzalez-Baron et al.[14]	36	Cisplatin/tegafur	22	94
Gonzalez-Baron et al.[14]	22	Carboplatin/tegafur	33	62
Feliu et al.[15]	43	Carboplatin/tegafur/calcium folinate (leucovorin)	26	59
Gonzalez-Larriba et al.[16]	34	Cisplatin/5-FU	21	73
	33	Cisplatin/tegafur/uracil (UFT®)	18	79

CR = complete response; **OR** = overall response; **5-FU** = fluorouracil.

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twice daily) and eniluracil (20mg twice daily). Administration by gastric tube was not allowed. RT was given concomitantly with these drugs at 150 cGy twice daily, and cycles were repeated every other week to a total of 6000 to 7500 cGy. DPD was virtually completely inhibited at these doses of eniluracil. Serum 5-FU concentrations were approximately equivalent to those attained with 5-FU infusion at 800 mg/m^2. The dose-limiting toxicity was myelosuppression during cycles 4 and 5. As a result, the recommended phase II dose in this setting was 5 mg/m^2 5-FU twice daily with 20mg eniluracil twice daily.[19]

2.2 Oral Etoposide in HNC

Oral etoposide is commonly used as part of curative or palliative regimens in several diseases including small cell lung cancer, testicular cancer, and carcinoma of unknown primary origin.[20-22] The role of oral etoposide in HNC has been less well studied. Etoposide, given intravenously as a single agent, showed only minor activity in 2 phase II studies of previously treated HNC patients.[23,24] There has been one study of oral etoposide given as a single agent in HNC.[25] In this study, 16 patients who had previously received a median of 3 chemotherapy drugs received 100 mg/m^2 of oral etoposide for 5 days, repeated every 3 weeks. There were no responders in this study. Since heavily pretreated patients were studied, it is difficult to assess with certainty whether single agent oral etoposide or intravenous etoposide is active in this disease.

Several other studies have used intravenous etoposide as part of a combination regimen for HNC patients. In 2 studies, etoposide was added to cisplatin and bleomycin. The response rate in these small studies appeared to be slightly higher than would be expected with only cisplatin- or bleomycin-containing regimens. However, the toxicity was generally rather high, and the incremental benefit of the etoposide was difficult to assess.[26-28] Two additional studies compared cisplatin alone with the combination of cisplatin and oral etoposide with or without 5-FU.[29,30] The response rates were equivalent with or without etoposide in one study[30] and improved with etoposide in the other.[29] In the latter study, etoposide was given both intravenously and orally. On the basis of these results, additional studies are warranted to determine the efficacy of etoposide for the treatment of HNC.

2.3 Oral Hydroxycarbamide in HNC

Hydroxycarbamide (hydroxyurea), a ribonuclease reductase inhibitor, has had little role as a single agent for the systemic treatment of HNC, although some early studies have suggested single agent activity.[31] Results of studies of single agent hydroxycarbamide as a radiosensitiser suggest an enhancement of activity and survival over RT alone.[31-33]

The combination of hydroxycarbamide and 5-FU has been extensively studied at the University of Chicago. The rationale for this combination is based both on theoretical and extensive *in vitro* study. Hydroxycarbamide modulates 5-FU by depleting deoxyuridine monophosphate (dUMP). This enhances the binding of 5-fluorodeoxyuridine mono-phosphate (5-FdUMP) to thymidylate synthase, thereby enhancing the activity of 5-FU. There is *in vitro* evidence of both additive and synergistic activities of these 2 drugs in HNC.[31,34-36]

The addition of hydroxycarbamide to 5-FU may overcome resistance to 5-FU-containing regimens. In one small study, *l*-leucovorin (100 mg/m^2 on day 1), 5-FU (450 mg/m^2 on day 1), and hydroxycarbamide (1000 mg/m^2 on day 1) were administered to 21 patients. This regimen was repeated weekly for 6 weeks. All 21 patients were previously treated with cisplatin, 5-FU, and calcium folinate, but were either unresponsive or showed progression while on treatment. Surprisingly, the response rate in the study was 23% (5 of 21 patients) with a median duration of response of 6.5 months, although all 5 responders had previously responded to chemotherapy.[37]

On the basis of the above rationale, the University of Chicago piloted a phase I study from 1986 to 1988 of 5-FU, hydroxycarbamide, and RT (the

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Table III. University of Chicago studies with hydroxycarbamide (hydroxyurea) as a radiosensitiser in head and neck cancer. The 6 regimens and 10 studies are from 1986-1998

Study	Years	Total no. of patients	Patient population	Phase	5-FU dose (mg/m^2) x 5 days	Hydroxycarbamide dose (mg) x 11 doses	RT dose (cGy)	Other drugs
FHX[38]	1986-88	39	(17 Re-RT)	I	800	1000[a]	200	
PFL, IFN-FHX[39,40]	1989-93	161	Stage 4[b]	II	800	1000	200	PFL/IFN induction x 3
$FHX_{2,3}$ [41]	1991-96	44	Stage 2,3	II	800	1000	200	
$CFHX_{I}$ [42]	1989-93	69	(29 Re-RT)	I	800	1000[a]	150 bid[a]	Cisplatin 100 mg/m^2 cycle 1,3,5
$CFHX_{II}$ [43]	1993-95	64	Stage 4[b]	II	800	1000	150 bid	Cisplatin 100 mg/m^2 cycle 1,3,5
$TFHX_{Ia}$ [44]	1993-95	55	(25 Re-RT)	I	600a	500[a]	150 bid[a]	(i) Paclitaxel 20 mg/m^2/day continuous x 5 days[a]
$TFHX_{Ib}$ [45]	1995-97	54	(25 Re-RT)	I	600	500	150 bid	(ii) Paclitaxel 100 mg/m^2, day 1[a]
$TFHX_{IIa}$ [46]	1995-97	69	Stage 4[b]	II	600	500	150 bid	(i) Paclitaxel
$TFHX_{IIb}$ [47]	1997-	61	Stage 4b	II	600	500	150 bid	(ii) Paclitaxel
$FH2X_{2,3}$ [c]	1997-	12	Stage 2, 3	II	800	1000	150 bid	

a Dose escalation of drug. Dose given is recommended phase II dose.

b Mixed resectable and unresectable.

c Bruce E. Brockstein, unpublished data.

bid = twice daily; **CFHX** = cisplatin plus FHX; **FHX** = 5-FU, hydroxycarbamide and RT; **5-FU** = fluorouracil; **IFN** = interferon-α; **PFL** = cisplatin, 5-FU, calcium folinate (leucovorin); **RT** = radiotherapy; **Re-RT** = repeat radiotherapy; **TFHX** = paclitaxel plus FHX; **FH2X** = 5-FU, hydroxycarbamide and twice-daily RT.

FHX regimen) in previously treated and poor-risk HNC patients.[38] In this initial study, 39 patients were treated with infusional 5-FU and oral hydroxycarbamide with once-daily RT. 17 of the patients had received prior RT. The recommended phase II dosages were as follows: 5-FU, 800 mg/m^2 by continuous infusion on days 1 to 5; hydroxycarbamide, 1000mg orally twice daily for 11 doses, beginning the night before RT; and RT, 180 to 200 cGy on days 1 to 5. Cycles were repeated after a 9-day rest until RT was complete. The 2-year local control rates in previously treated and untreated patients were 18 and 82%, respectively. Thus, this regimen demonstrated curative potential for locoregionally advanced HNC. FHX has subsequently served as the backbone for treatment of more than 500 HNC patients in 10 studies (table III).[38-47]

In the next trial, induction chemotherapy was given prior to the FHX regimen in an attempt to allow organ preservation and to minimise the risk of systemic relapse.[39,40] A total of 161 patients (94% stage 4, 69% N2/3) were treated with neoadjuvant cisplatin, 5-FU, and calcium folinate [(PFL) half with the *l*-stereoisomer of calcium folinate (leucovorin)] plus interferon (IFN)-α. In this study, the PFL regimen consisted of cisplatin (100 mg/m^2 on day 1), 5-FU (640 mg/m^2/day continuous infusion on days 1 to 5), calcium folinate (100mg orally every 4 hours on days 1 to 6) or *l*-leucovorin (300 mg/m^2/day on days 1 to 5), and IFNα (2 MU/m^2 subcutaneously on days 1 to 6). The CR to induction was 60%. Patients then proceeded to optional surgery followed by FHX (5-FU, 800 mg/m^2/day continuous infusion for 5 days; hydroxycarbamide, 1000mg orally every 12 hours for 11 doses; and RT, 200 cGy/day concurrently for 5 days). Cycles were repeated every 14 days to a total dose of >7000 cGy. Surgical

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resection was necessary in only 62 patients (14 composite resections, 27 limited procedures of the primary site, and 59 neck dissections). With a minimum follow-up of 4 years, local recurrence was 21%, and distant recurrence only 9%. Overall survival at 5 years was 50%. Although this study was not randomised, survival results were extremely encouraging compared with the 10 to 40% survival expected in this population with conventional therapy.

In the studies that followed,[41-47] induction chemotherapy was eliminated since it had been shown in numerous randomised studies to add cost, time, and toxicity to the regimen with little or no survival benefit.[7,8,48] The development of the FHX regimen then focused on improving locoregional and distant control rates by adding an additional systemically active agent (cisplatin and then paclitaxel) and utilising hyperfractionated RT (150 cGy twice daily). These regimens are detailed in table III. Although the exact contribution of hydroxycarbamide is not measurable without a randomised trial, the locoregional control rates of 80 to 90%, which have been realised in the 3 phase II trials analysed to date,[39-41,43] clearly exceed those seen with RT alone or with RT and single agent 5-FU.[48]

3. Candidate Drugs for Use in HNC

Several other oral drugs that are either already approved or under development are good candidate drugs for use in HNC. BMS-182751 (JM-216), an oral platinum complex, is currently under investigation in phase II studies.[49] Two other oral fluoropyrimidines, capecitabine[18,50] and S-1,[18] offer potential advantages over oral 5-FU. They may be useful in HNC in settings where continuous infusion 5-FU is currently used. Finally, methotrexate and cyclophosphamide, both with minor activity in HNC and available orally, have not been adequately studied in the oral form in HNC.

4. Conclusions

The emergence of multiple new oral chemotherapy drugs has created the prospect for simplified and/or more effective therapy for HNC. Hydroxycarbamide has been shown to be effective as a radiosensitiser when administered with intravenous 5-FU. Tegafur/uracil and oral 5-FU with eniluracil have shown promising activity in HNC. Several other drugs under development, including BMS-182751, capecitabine, and S-1, though not currently studied, may also have a role in the treatment of HNC.

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