CLINICAL STUDY PROTOCOL

PHASE II TRIAL OF CARBOPLATIN, UFT AND CONCURRENT RADIOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK CANCER

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1.0 Title

"Phase II Trial of Carboplatin, UFT, and Concurrent Radiotherapy in Locally Advanced Head and Neck Cancer"

2.0 Objectives

2.1 To assess the therapeutic efficacy of Carboplatin and UFT given concurrently with radiation in locally advanced head and neck cancer. The primary endpoints of therapeutic efficacy are response rate, time to disease progression and survival time.

2.2 To assess the qualitative and quantitative toxicity of these treatment.

3.0 Background

Head and neck cancer represents a heterogenous group of disease. Generally, it includes squamous cell carcinoma of the oral cavity, pharynx and larynx. It is estimated that, worldwide more than 500,000 new cases are diagnosed annually.[1] Surgery and radiation therapy and in combination are the standard treatment option for squamous cell carcinoma of the head and neck. Early stage disease (T_{1-2}, N_0, M_0), can be treated with curative intent by surgery or radiotherapy. This goal would be achieved in more than 80% of patients with stage I disease and more than 60% of patients with stage II disease.[1] Approximately, more than two-thirds of head and neck cancer patients would initially present with stage III or IV disease. Standard therapy for these patients usually includes surgery, radiation therapy, or both. Despite aggressive local therapy, 50 - 60% of these patients would ultimately develop local recurrence and 30% would develop distant metastasis. The overall survival rate is 40% for patients whose tumors are completely resected and only 20% for those with unresectable tumors treated with radiotherapy alone.[2] According to the Radiation Therapy Oncology Group (RTOG) tumor registry, patients with advanced bulky disease (T_3, T_4, N_2 or N_3) have local control ranging from 30% - 40% following radiation therapy alone and median survival of $\leq$ 1 year.[3] More importantly, patients with stage IV disease usually have a median survival of less than 10 months, and fewer than 25% of these patients remain alive at 3 years.[4] With these unsatisfactory results obtained in treating locally advanced head and neck cancer, chemotherapy has been introduced and studied extensively with the goals of improved local control, reduction of distant metastasis and improved overall survival.

The role of chemotherapy has expanded from its accepted indication as palliative therapy for recurrent and metastatic disease to an integrated part of primary curative therapy. Chemotherapeutic agents that are active in squamous cell carcinoma of head and neck include cisplatin, carboplatin, fluorouracil (5-FU), methotrexate, bleomycin, cyclophosphamide, hydroxyurea, mitomycin, doxorubicin, and paclitaxel.[5] The response rates vary from 10 - 40%. Cisplatin-containing regimen, mainly cisplatin and 5-FU, given as induction therapy before radiation usually gives high response rates but this treatment has not yet translated into prolonged survival. With the exception of treating laryngeal cancer aiming for organ preservation, induction chemotherapy has no role yet as a standard therapy for head and neck cancer.[6] Concomitant chemoradiotherapy has been pursued extensively and demonstrated a significantly better locoregional control and a trend toward better survival. The mechanisms which chemotherapy potentiates the cytotoxic effects of radiation include inhibition of sublethal damage repair, hypoxic cell sensitization and cell-cell

synchronization. The interaction between chemotherapy and radiotherapy are defined as 1) spatial cooperation or independent action of each modality, 2) toxicity independence which allows full dose delivery of each modality without additive toxicity, 3) chemoprotection or protection of normal tissues allowing higher doses of radiotherapy to be delivered, and 4) chemosensitization or enhancement.[6] Combination chemotherapy with concomitant radiation therapy has been compared with induction chemotherapy (using the same dose) followed by radiation therapy. All 3 trials conducted in this fashion indicated a superior disease-free or overall survival for the concomitant treatment group. In the SECOG I study (South East Co-operative Oncology Group) in advanced head and neck cancer, concomitant administration of vincristine, bleomycin, methotrexate, 5-FU and radiation demonstrated a significant improvement in disease-free survival as compared to the sequential administration of chemoradiotherapy of the same regimen.[7] Adelstein used cisplatin and 5-FU simultaneously with radiation in locally advanced head and neck cancer and found significant improvement in disease-free survival at 41 months (60% vs 39%) when compared with sequential chemoradiotherapy.[8] Meslano used vinblastine, bleomycin, methotrexate concomitantly with radiation versus sequential chemoradiotherapy in advanced inoperable head and neck cancer and reported a superior 4 year overall survival (22% vs 10%) favoring the concomitant arm.[9]

Carboplatin is platinum analogue that was introduced in 1981 because of its lesser toxicity, equivalent biochemical selectivity and antitumor spectrum relative to cisplatin.[10] Specifically, the antitumor activity of carboplatin is comparable to that of cisplatin in patients with recurrent and metastatic head and neck cancer.[11, 12] In vivo and in vitro studies also demonstrated a synergistic effect of carboplatin and radiation.[13, 14, 15] Zamboglou conducted phase I study in inoperable squamous cell carcinoma of head and neck and defined the maximum tolerable dose of carboplatin as 70 mg/m^2 (d 1 - 5) when given simultaneously with radiation.[16] Subsequently in phase II study in advanced head and neck cancer, carboplatin 60 or 70 mg/m^2 (d 1 - 5 and d 29 - 33) was given concurrently with radiation. For patients who received 70 mg/m^2 of carboplatin, grade 3 and 4 leukopenia occurred in 19% and grade 3 and 4 thrombocytopenia in 12.5%. With dose reduction to 60 mg/m^2, grade 3 and 4 leukopenia developed in only 4.5% and grade 3 thrombocytopenia in 6.8%. In this study, 69% CR and 30% PR were achieved and actuarial 1- and 2- year survival rates were 77% and 53% respectively. Weekly carboplatin given concurrently with radiation was also tested in locally advanced head and neck cancer. Eisenberger used carboplatin 60, 75 or 100 mg/m^2/week for 6 weeks or monthly (400 mg/m^2) together with conventional radiotherapy (5 daily fractions of 1.8 - 2.0 Gy/wk x 6 - 7 weeks plus additional tumor boost as indicated).[17] This study indicated that the dose of 100 mg/m^2/wk of carboplatin was reasonably well tolerated and all treatment could be given without significant delays or dosage reduction. Myelotoxicity was mild and easily managed, and the degree of mucositis was similar to that seen with radiotherapy alone. However, with monthly schedule, severe myelosuppression requiring blood component support was observed in 3 out of 4 patients which prompted the investigator to close this arm of study prematurely. Of 30 patients entered this weekly and monthly schedule, 52% CR was obtained. The median time to progression and median

survival for all patients were approximately 8 and 12 months, respectively.

Volling used carboplatin an escalating dose level: 20, 30, 40, 50, 60 mg/m^2 on day 1 to 4 in weeks 1, 2, and 5 and on another 2 days in weeks 6 concurrently with radiation (58.8 - 67.2 Gy) in unresectable squamous cell carcinoma of the head and neck.[18] Dose-limiting toxicity was myelosuppression, with grade 3 and 4 leukopenia occurring in 83% of patients treated with carboplatin 60 mg/m^2 and 67.2 Gy radiation. In patients treated with carboplatin 50 mg/m^2 and 67.2 Gy radiation, no grade 4 myelosuppression developed and toxicity was generally well tolerated. Mucositis was the most important nonhematologic toxicity and occurred in all patients regardless of the carboplatin dose level. With good preparation for prophylactic PEG, the treatment schedule was not interrupted by this side effect. No evidence of nephrotoxicity, ototoxicity, or neuropathy was observed in this study.

UFT is a combined drug of tegafur and uracil in a 1:4 molar ratio. The antineoplastic effect of UFT is due to 5-FU which is gradually converted from tegafur. Uracil inhibits the degradation of 5-FU, permitting the maintenance of 5-FU, particularly in tumor tissue. Thus, uracil enhances the antitumor activity of tegafur. Inuyama reported a phase II study of UFT in head and neck cancer from 10 institutions in Japan.19 UFT was administered at a dose of 600 mg/day. Among 60 evaluable cases, 13%CR and 17%PR were observed. Side effects developed in 40.3% with anorexia being the most frequent occurrence (32.8%), followed by nausea and vomiting (16.4%), stomatitis (7.5%), and diarrhea (6%). Only one patient experienced severe bone marrow suppression.

Valverde used neoadjuvant chemotherapy with cisplatin and 5-FU versus cisplatin and UFT in unresectable stage III or IV squamous cell carcinoma of head and neck.[20] Patients were randomized to receive either cisplatin 100 mg/m^2 d 1 and 5-FU 1000 mg/m^2 d 2-6 every 21 days or cisplatin 100 mg/m^2 d 1 and UFT 300 mg/m^2/d orally d 1-20 every 21 days. Patients with response to chemotherapy would proceed to receive radiotherapy. Both schedules had similar outcome in terms of local control (21%CR for cisplatin + 5-FU; 19%CR for cisplatin + UFT), progression-free survival, and overall survival. It appeared that the UFT/cisplatin regimen was better tolerated, with a lower incidence of emesis, mucositis, and phlebitis.

Based on compiled data from the literature, carboplatin/UFT has the advantage of easy outpatient administration and can be administered safely to patients with impaired renal function using the Calvert formular.[21] We, therefore, selected carboplatin, UFT and concurrent radiation therapy to be administered in patients with locally advanced head and neck cancer and this study will be conducted as a phase II trial.

4.0 Drug Information

4.1 Carboplatin

4.1.1 Human toxicity :

Side effects of carboplatin include myelosuppression, nausea, vomiting, loss of appetite. Rare toxicity include gross hematuria, hyponatremia, aguesia, allergic reaction, peripheral neuropathy, venoocclusive disease, loss of hair, liver damage, kidney damage, hearing loss, dizziness and blurred vision.

4.1.2 Pharmaceutical Data :

Formulation : Carboplatin is supplied as a sterile lyophilized powder

available in single dose vials containing 150 mg, and 450 mg of Carboplatin for administration by intravenous injection. Each vial contains equal parts by weight of Carboplatin and mannitol. Immediately before use, the content of each vial must be reconstituted with either Sterile Water for Injection, USP; 5% Dextrose in Water, or 0.9% Sodium Chloride Injection, USP; according to the following schedule:

Vial Strength	Diluent Volume
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a Carboplatin concentration of 10 mg/ml with 5% Dextrose in Water or 0.9% Sodium Chloride Injection, USP.

Storage and Stability : Unopened vials for injection are stable for the life indicated on the package when stored at controlled room temperature 15 - 30 degrees Celsius and protected from light. When prepared as directed, Carboplatin solutions are stable for 8 hours at room temperature. Since no antibacterial preservatives is contained in the formulation, it is recommended that Carboplatin solutions be discarded 8 hours after dilution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Administration : Intravenous

Supplier : CBDCA is commercially available and partly supported by Bristol-Myers-Squibb (Thailand)

4.2 UFT

4.2.1 Human toxicity :

Commonly observed side effects include gastrointestinal (anorexia, nausea, vomiting, diarrhea), and hematologic (leukopenia, thrombocytopenia). Anorexia, nausea, and vomiting are frequently observed at 1-3 weeks after administration. Diarrhea is frequently observed at 2-6 weeks. Leukopenia and thrombocytopenia are observed beginning at 2 weeks and frequently observed at 5-6 weeks. Erythrocytopenia is frequently observed at 4-12 weeks. Rare toxicity includes jaundice, hematuria, proteinuria, gastric or duodenal ulcer, somnolence, urinary incontinence, alopecia, dermatitis, chest pain, epistaxia, and conjunctival congestion.

4.2.2 Pharmacological Data :

Formulation : [Its molecular formula is C8H9FN2O3 (tegafur) and C4H4FN2O2 (uracil)] Its chemical name is 1-(2 tetrahydrofuryl)-5-fluorouracil and 2, 4 (1H, 3H)-pyrimidinedione. Each UFT capsule contains tegafur 100 mg and uracil 224 mg. The molecular weight of tegafur is 200.17 and of uracil is 112.09. UFT is available as white, odorless fine granules or bitter odorless powder in opaque white capsules.

Administration : orally

Supplier : UFT is commercially available and partly supported by Thai Otsuka Pharmaceutical. (Thailand)

4.3 GM-CSF (Leucomax ®) will be partly supported by Schering-Plough (Thailand)

4.4 Ondansetron (Zofran ®) will be partly supported by Glaxo Wellcome (Thailand)

5.0 Selection of Patients

5.1 Inclusion Criteria :

5.1.1 All patients must have histologically or cytologically confirmed squamous cell carcinoma of the head and neck region i.e. oropharynx, hypopharynx, larynx. (primary sites at nasopharynx and oral cavity will be excluded) Initial clinical / pathological stage must be specified.

5.1.2 Patients must have locally

advanced inoperable head and neck cancer stage III, IV.

5.1.3 Patients must have ECOG performance status of 0, 1, or 2.

5.1.4 Patients must have measurable disease by physical exam. or roentgenographic study.

5.1.5 Patients must have adequate bone marrow, liver, and renal functions defined as follows:

Hemoglobin ≥ 10 mg%,
WBC ≥ 4,000/mm3, platelet ≥ 100,000/mm3 (granulocyte ≥ 1,500/mm3)

Hepatic : bilirubin ≤ 2.0 mg%, SGOT, SGPT, alkaline phosphatase in normal range

Renal : creatinine ≤ 1.5 mg/ml

5.1.6 Age ≥ 18 years, ≤ 65 years

5.1.7 No prior chemotherapy, radiotherapy or biologic response modifier.

5.1.8 No evidence of distant metastasis.

5.2 Exclusion Criteria :

5.2.1 Concomitant malignant disease in other parts of the body.

5.2.2 Active uncontrolled infection.

5.2.3 Pregnant or lactating women.

5.2.4 Medical or psychiatric illness that compromise the patients' ability to complete the study.

5.2.5 Expected survival <6 months.

5.3 Withdrawal Criteria :

A patient will be withdrawn from the study if any of the following events occur :

5.3.1 Interruption of therapy resulting in delay of scheduled therapy for greater than 14 days except when as a result of resolution or toxicity.

5.3.2 Intolerable adverse effects that are judged by the investigator to be either physically or psychologically detrimental to the patient.

5.3.3 Patient decision to discontinue treatment.

5.3.4 Unresolved or recurrent grade III or IV toxicity.

5.3.5 A serious systemic allergic response to any of the study drugs manifested by angioedema, bronchoconstriction or anaphylaxis.

6.0 Conduct of Study

6.1 Schedule of Activities and Evaluations

All screening tests, examinations, and procedures must be completed within 14 days prior to the initial dose. Results of all screening evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed prior to beginning treatment.

Before treatment begins, the patient must be thoroughly informed about all aspects of the study including the study visit and activities schedule, and all regulatory requirements for informed consent must have been satisfied.

Clinical evaluations : Complete medical history, including but not limited to data of diagnosis of cancer, procedures and tests used for staging and current extent of disease.

Laboratory Procedures - Hematology

: WBC, Differential count, Platelet count, Hemoglobin, Hematocrit

: Serum chemistries

: BUN, Creatinine, Alkaline phosphatase, Calcium, Total bilirubin, Phosphorous, Total serum protein, Albumin, LDH, SGOT, SGPT

: Serum electrolytes (sodium, potassium, chloride, bicarbonate)

Diagnosis Procedures :

: Chest X-ray

: C.T. Scan (optional)

6.2 Randomization : Single arm, nonrandomization

6.3 Chemotherapy Schedule :

Carboplatin (AUC = 2) will be given as intravenous infusion in 1 - 2 hours every week for 6 weeks starting from day 1 of treatment concurrently with radiation therapy. Pretreatment antiemetic therapy (Zofran 8 mg IV.) is generally recommended.

Carboplatin dose (mg) =
AUC (GFR + 25)

Glomerular filtration rate (GFR) =
$\frac{(140 - \text{age}) \ (\text{weight in kg})}{\text{serum creatinine (mg/dl)} \times 72}$ ml/min

15% reduction for woman

UFT 400 mg/day in two divided dose (A.M. & P.M.) will be given orally (one hour before or after meal) from day 1 until the end of radiation therapy

6.4 Radiation Therapy Schedule :

Equipment : Megavoltage equipment with a Source Skin Distant (SSD) of 80 cm. (SAD for isocentric technique) or greater will be used. (Megavoltage machine with an energy equal to Cobalt 60 or higher)

General Guideline

Radiation Field : The treatment volume includes primary tumor with a 1.5 cm. minimum margin, the neck nodes, and the supraclavicular fossa. The primary tumor and the upper neck nodes are treated with paralleled opposed portals. Anterior field may be added if complete coverage of the tumor could not be accomplished by lateral field. In this situation, computer treatment planning is mandating. The lower neck nodes are treated with anterior field with appropriate placement of spinal cord block. The lower margin of the upper neck field abuts the superior margin of the lower neck field. All patients will be simulated and films are submitted for review upon request.

Dose & Fractionation :

: All doses will be specified to the midpoint central axis.

: The dose to the supraclavicular nodes will be calculated to 3 cm. depth.

: The spinal cord dose will not exceed 45 Gy at the midline.

: Initial on-spinal cord fields are treated with 1.8 - 2.0 Gy. fractions until the spinal cord dose reaches 45 Gy.

: The off-spinal cord fields are treated with 1.8 - 2.0 Gy fractions to 60 Gy. After that, the field could be reduced to cover only the primary tumor with a minimum 1 cm. margin. The final tumor dose ranges from 66 - 74 Gy.

: Clinically disease-negative supraclavicular field receives 50 - 54 Gy in 25 - 30 fractions. Clinically palpable node could be boosted up to 66 - 74 Gy.

: The cervical posterior strip is boosted with electrons of appropriate energy in all patients with involvement of posterior cervical area to a total dose of 66 - 74 Gy.

: All treatment fields are irradiated at each session.

Specific Guideline for Each Primary Site

Hypopharynx: The treatment field

should encompass the nasopharynx, oropharynx, hypopharynx, and upper cervical esophagus, because of the propensity of tumor spreading submucosally. Lateral beam direction generally can be used to encompass the tumor with adequate superior and inferior margins if the patient's shoulders are depressed. If lateral beam direction inadequately encompass the tumor, then anterior or anterior oblique fields with wedges are advised. If any palpable cervical lymph nodes are present, fields should encompass anterior and posterior cervical triangles, and the anterior margin is just sufficient to irradiate the oropharynx, thereby shielding the oral cavity and lessening the mucosal area irradiated.

Tonsillar fossa and faucial arch : The standard arrangement consists of lateral portals that include the primary tumor, buccal mucosa, gingiva, base of tongue, nasopharynx, lateral/posterior pharyngeal wall, upper and posterior cervical lymph nodes. The superior border is placed at zygomatic arch. The middle and internal ear should be carefully shielded posteriorly. The port extends posteriorly around the external auditory canal to a line joining the tip of the mastoid to above the foramen magnum. The anterior margin is placed clinically with at least a 2 cm. margin beyond any clinical evidence of disease. Inferiorly, the port extends to the thyroid notch except in patients who have downward extension of tumor with pharyngeal wall involvement, in which case the margin must be placed below that level. Posteriorly, the posterior cervical lymph nodes should be covered; a small amount of subcutaneous tissue should be spared to avoid fall-off, except in patients with gross cervical lymphodenopathy in which a fall-off is appropriate to avoid geographic miss.

The lower neck is treated with a standard anteroposterior portal. A midline block can be used to shield the larynx and spinal cord. However, if lymph nodes are present in this area, only a small block to shield the larynx and a portion of spinal cord is used.

Base of tongue : Ports should extend superiorly to base of skull (floor of sphenoid sinus) to include the retropharyngeal lymphaties, anteriorly to include the faucial arch and a portion of the oral tongue, inferiorly to include the supraglottic larynx, and posteriorly to include the posterior cervical triangle. The primary tumor and both sides of upper neck are irradiated through lateral fields, and both sides of lower neck are irradiated through a single anteroposterior field with a midline block.

Supraglottic and glottic larynx : Beam direction is usually lateral except for patients with short, thick, flat necks who require anterior oblique beam direction to avoid the shoulder. Patients are treated in a supine posterior with a roll under the shoulders to hyperextend the neck and expose the larynx

Due to significant incidence of lymphatic metastasis in large transglottic and supraglottic tumors, both sides of the neck as well as the larynx are irradiated. Fields extend from the inferior margin of the mandible and mastoid tip to the clavicle and encompass the anterior and posterior cervical triangles as well as the larynx.

Dose modification

: Hematologic toxicity

WBC	ANC	Platelets	Management
> 3,500	> 1,500	≥ 100,000	Give full does
2,500 - 3,500	1,000 - 1,500	< 75,000-100,000	Decrease chemotherapy dose 50%
< 2,500	< 1,000	<75,000	Omit chemotherapy and RT

GM - CSF (Leucomax®) will be given if there is treatment indication (Appendix: E and F : ASCO guideline and individual judgement)

: Mucositis

The occurrence of grade 3 mucositis at any time is an indication to discontinue UFT, carboplatin and radiation therapy until the symptom subsides.

: Diarrhea

For grade 2 diarrhea, give 75% of UFT. For grade 3 diarrhea, UFT is discontinued. However, radiation therapy and carboplatin may be continued.

The treatment is completed as per protocol for rest periods up to 14 days. If the break exceeds 14 days, the patient will be taken off protocol. He/she will then complete treatment at the discretion of his/her physician but the patient will be followed and included in the analysis.

7.0 Evaluation During Therapy

7.1 Physical examination is performed weekly to document the local response.

7.2 CBC and platelet count are determined weekly.

7.3 BUN and creatinine are determined biweekly.

7.4 Documentation of radiation side effects is performed weekly using RTOG criteria.

7.5 Adverse events will be documented using WHO criteria.

8.0 Follow up After Completion of the Protocol

Criteria for response, progression and relapse are as follows:

8.1 Tumor Response

A patient will be considered evaluable for tumor response and drug efficacy if he or she has had a minimum of two courses unless disease progression is observed.

8.1.1 Complete Response :

Complete resolution in all measurable or palpable tumors and no appearance of new lesions documented on two occasions at least three weeks apart. In patients whose tumor has been evaluated by physical examination with radiologic confirmation, radiologic confirmation of complete response should be made on the second of the two occasions. The clinical examination (e.g. for lesions located in the head and neck) will override the radiological examination (e.g. inability or radiographic tests to distinguish residual disease from edema and scar formation.

8.1.2 Partial Response :

A reduction 50% in the sum of the products of the two longest perpendicular diameters of measurable tumors and no appearance of new lesions, documented on two evaluations at least three weeks apart.

8.1.3 Minimal Response :

A reduction 25% but <50% in the products of the two longest perpendicular

diameters of measurable tumor and no appearance of new lesions, documented on two evaluations at least three weeks apart.

8.1.4 Stable Disease :

Tumor reduction less than minimal response but not demonstrating progression as defined in (Section 8.1.5)

8.1.5 Progressive disease is defined by either of the following:

: Appearance of new areas of malignant disease

: Increase in previously measurable lesions (excluding bone) by greater than 25% in the product of the two longest perpendicular diameters.

8.2 Time to tumor progression will be different as the time from first dose of therapy until there is progressive disease.

8.3 Response durations will be defined as the time from response (not the beginning of treatment) until there is progressive disease.

8.4 Survival Durations : The survival of patients will be measured from first dose of therapy.

8.5 All toxicities encountered from chemotherapy during the study will be evaluated according to the grading system (0 - 4) in Appendix D and recorded prior to each course of therapy. Duration of toxicity and treatment will be recorded. Radiation Therapy toxicity will be recorded according to Appendix B and C.

8.6 Follow - up assessment are to be performed every month during the first year, every 2 months during the second year, then, every 6 months for the next 3 years, and annually after the fifth year. The following parameters will be evaluated.

a. primary tumor site
b. regional nodes
c. metastatic visceral spread
d. treatment complication

9.0 Withdrawal of Patients from the Study

A patient will be withdrawn from the study for any of the reason listed in Section 5.3. Any patient with an allergic reaction or severe degree of intolerance to the study medication should be observed as long as necessary by the treating physician. The day treatment is terminated, for whatever reason, will be considered the "day off study". Patient removed from the study for toxicity should be re-evaluated within two weeks after the last injection and followed until the toxicity has resolved.

10.0 Statistical Analysis

Response rate (CR + PR) will be calculated along with confidential interval. Actuarial survival curve will be used for survival time and time to disease progression.

References

1. Vokes EE, Weichselbaum RR. Lippman SM, Hong WK. Head and Neck Cancer. N Engl J Med 1993; 328 : 184 - 194.
2. Hong WK, Dimery IW. Overview of com bined modality therapies for head and neck cancer. J Natl Cancer Inst 1993; 85 : 95 - 111.
3. Marcial VA, Pajak TF, Kramer S, et al. Radiation Therapy Oncology Group (RTOG) Studies in head and neck cancer. Semin Oncol. 1988; 16 : 39 - 60.
4. Parsons JT, Mendenhall WM, Million RR, et al. The management of primary cancers of the oropharynx: Combined treatment or irradiation alone ? Semin Radiat Oncol 1992; 2 : 142 - 148.

5. Al-Sarraf M. Head and neck cancer : che motherapy concepts. Semin Oncol 1988; 15 : 70 - 85.
6. Stupp R, Weichselbaum RR, Vokes EE. Combined modality therapy of head and neck cancer. Semin Oncol 1994; 21 : 349 - 358.
7. A randomized trial of combined multidrug chemotherapy and radiotherapy in advanced squamous cell carcinoma of the head and neck: an interim report from the SECOG participants. Eur J Surg Oncol 1986; 12 : 289 - 295.
8. Adelstein DJ, Sharan VM, Earle AS, et al. Simultaneous versus sequential combined technique therapy for squamous cell head and neck cancer. Cancer 1990; 65 : 1685 - 1691.
9. Merlano M, Corvo R, Margarino G, et al. Combined chemotherapy and radiation therapy in advanced inoperable squamous cell carcinoma of the head and neck : the final report of a randomized trial. Cancer 1991; 67 : 915 - 921.
10. Muggia FM. Overview of carboplatin : Replacing complementing and extending the therapeutic horizons of cisplatin. Semin Oncol 1989; 16 : 7 - 13. (supp. 5)
11. Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous cell carcinoma of the head and neck : A Southwest Oncology Group Study. J Clin Oncol 1992; 10 : 1245 - 1251.
12. Eisenberger M, van Echo D, Aisner J. Carboplatin : The experience in head and neck cancer. Semin Oncol 1989; 16 : 34 - 41.
13. Schwachofer JHM, Crooijmans RPAM, Hoogenhout J. Effectiveness in inhibition of recovery of cell survival by cisplatin and carboplatin : influence of treatment sequence. Int J Radiat Oncol Biol Phys 1994; 20 : 1235 - 1241.
14. Pekkola-Heino K, Kulmala J, Grenman R. Carboplatin radiation interaction in squamous cell carcinoma cell lines. Arch Otolaryngeal Head and Neck Surg 1992; 118 : 1312 - 1315.
15. Yang LX, Douple EB, Wang HL. Irradiation enhances cellular uptake of carboplatin. Int J Radiat Oncol Biol Phys 1995; 33 : 641 - 646.
16. Zamboglou N, Schnabel T, Kolotas C, et al. Carboplatin and radiotherapy in the treatment of head and neck cancer: Six years' experience. Semin Oncol 1994; 21 : 45 - 53. (supp. 12)
17. Eisenberger M, Jacobs M. Simultaneous treatment with single-agent chemotherapy and radiation for locally advanced cancer of head and neck. Semin Oncol 1992; 4 : 41 - 46. (supp. 11)
18. Volling P, Staar S, Achterrath W, Muller RP. Phase I/II study of simultaneous carboplatin and radiotherapy in unresectable squamous cell carcinoma of the head and neck. Semin Oncol 1992; 19 : 66 - 71. (supp. 2)
19. Inuyama Y, Fujii M, Mashno S, et al. Clinical effect of UFT for head and neck cancer. Cancer and chemotherapy 1983; 10 : 90 - 96.
20. Valverde JJ, Ganzale JI. Neoadjuvant chemotherapy with cisplatin and 5-FU versus cisplatin and UFT in advanced squamous head and neck cancer. Proc. ASCO 1993; 12 : 281.
21. Calvert AH, Newell DR, Gumbsell LA, et al.Carboplatin : Prospective pharmacokinetically guided dose-escalation in relation to renal function. Proc. ASCO 1987; 6 : 45.
22. Phase II Trial of Carboplatin, UFT, and Concurrent Radiotherapy in Locally Advanced Head and Neck Cancer