The Role of Chemotherapy in The Treatment for Locally Advanced Head and Neck Squamous Cell Carcinoma

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ABSTRACT

Head and neck carcinoma is the common malignancy in Thailand.[1] The treatment outcome, with standard surgery, radiation therapy or both combined treatment, is unsatisfied particularly for locally advanced disease. Furthermore functional damage and cosmetic deformity related to treatment are undesirable. Over past decade, chemotherapy was integrated as a part of combine treatment in an effort to improve therapeutic outcome and also creating an opportunity for organ sparing approach. This article review the evolution of chemotherapy usage in the treatment for locally advanced head and neck squamous cell carcinoma without metastasis.

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Head and neck carcinoma is the common cancer in Thailand.[1] In the past, the standard treatment are surgery, radiation therapy or both combined treatment. Despite optimal local therapy, 50-60% of these patients will ultimately develop local recurrences.[2] The survival is about 40% in patients whose tumor are completely resected.[3] Unfortunately, cure for unresectable head and neck squamous cell carcinoma treated with radiotherapy alone is uncommon. Most patients die from consequence of local disease progression and more than 30% will develop distant metastasis disease.[3] Furthermore, nearly one-third of those surviving their first cancer will encounter with the second primary malignancy such as esophageal cancer, thyroid cancer and other site of head and neck. This might be associated with the exposure of similar carcinogen. Besides the attempt to achieve disease control, the functional deficit and cosmetic deformity related to head and neck cancer treatment must be concerned. Locally advanced disease can often be difficult to resect due to invasion of critical vascular and neurological structures, and highly deforming that is not desirable. Multidisciplinary approach therefore became important consideration in treatment of locally advanced head and neck cancer. During the few decades, combined chemoradiotherapy have been developed in an effort to enhance locoregional disease control, reduce distant metastasis, and preserve anatomical functions. The possible synergistic effects of chemoradiotherapy are proposed.[2,4] (a) Prevention of emergence of resistant clones. The cancer cell, resisting to one modality, may be sensitive to a different modality. (b) Spatial co-operation, this concept is the basis of adjuvant therapy. It is referred to *"when one treatment is able to treat disease at one site, the other site such as distant subclinical disease is eradicated by the second modality of treatment, with improved results".* (c) Enhance tumor response, because the combination produces greater results than that expected from the individual effect of each treatment modalities. (d) Reduce radiation dose to prevent acute and long term toxicity. (e) Chemotherapy may inhibit the repopulation of tumor cells during fractionated irradiation.[4,5] Different approaches to integrate chemotherapy into combined modality treatments are categorized as follows:

1. Neoadjuvant chemotherapy
2. Adjuvant chemotherapy
3. Concurrent chemotherapy and radiotherapy

I. Neoadjuvant therapy

The treatment approach, first explored was neoadjuvant chemotherapy or induction chemotherapy followed by radiotherapy. It was well recognized that radiation therapy was more effective in patients with small initial tumor.[6] Since the best utilization of chemotherapy might be as the initial treatment approach to reduce the size of the tumor,

patients are likely to better tolerate chemotherapy according to undisturbed bone marrow reserve. Meanwhile, the presence of intact blood supply are subsequently higher tumor responsive with chemotherapy.[5] This produces an opportunity for an organ sparing management. Finally, induction chemotherapy allows for the earliest possible treatment of distant micrometastasis disease. Through evolution of the use of chemotherapy in locally advanced head and neck carcinoma, single agent therapy achieves complete response rates of less than 5%.[3,7] Therefore, it had little positive impact on survival outcome. Among the single chemotherapy, cisplatin gives the best overall response rate of approximately 25-30%[2,5]. Thus it become the backbone of multidrug therapy. Metrotrexate is the standard palliative chemotherapy for recurrent squamous cell carcinoma of head and neck. This agent is relatively non toxic and convenient, and also has a role in treatment for locally advanced head and neck cancer as initial chemotherapeutic agent. The response rate range from 14-52%[2,3], and it is the second most active agent. Combination chemotherapy regimens have been developed in an effort to improve response and survival rate. Several trials of metrotrexate and cisplatin based regimens have been studied.[8-12] The overall response rate more than 70% and complete response rate up to 24% with combination regimen had been observed. Subsequently, combination of cisplatin and 5 flurouracil (5FU) infusion gives the most dramatically change in treatment of head and neck squamous cell carcinoma. With this regimen, complete response rate more than 50% and overall response rate more than 90% were regularly remarked.[8-14] Unfortunately, most of these schedules failed to demonstrated any survival advantage for neoadjuvant treatment. Multiple explanations have been proposed including suboptimal chemotherapeutic regimen and small number of patients with heterogeneity. Recent studies, however, have employed standard 5FU and cisplatin regimen.[8-13] Only subset of inoperable patients were survival benefit.[9] Despite this failure of induction chemotherapy, several issues were concluded from phase II- III trial experiences as follows:

1. Significant tumor regression in 60-90% and complete response in 20-50% of patients with locally advanced squamous cell carcinoma of head and neck.
2. Up to two- third of these clinical complete responders will have no residual pathological evidence of disease.
3. Even in those patients achieving in a pathological complete response, a relapse is inevitable without definitive treatment (surgery and/ or radiation therapy).
4. Chemotherapy responders demonstrate further response to radiation therapy and chemotherapy non- responders do not.
5. Chemotherapy inducing response should be at least three courses of treatment.
6. Dose of chemotherapy appear to adversely affect for subsequent definitive management.
7. Patients with response to chemo-

therapy have better survival than those patients with partial response or non-responders.

8. When chemotherapy is a part of combined treatment, significant reduction in distant metastasis was observed.

9. No significant difference in an overall survival has been demonstrated with induction chemotherapy compared with surgery or radiation therapy alone.

10. With induction chemotherapy, organ preservation can be successful and quality of life was improved.

In summary, neoadjuvant chemotherapy in the treatment for locally advanced head and neck squamous cell carcinoma should be reserved for clinical trial. It should be limited to tumor that is amenable to surgery. Up front chemotherapy is use as selective test. Patients with good response are candidates for subsequent radiotherapy which the organ can be preserved. On the other hand, the poor responders subsequently undergo surgery with or without postoperative radiotherapy.

II. Adjuvant chemotherapy

The use of systemic chemotherapy after definitive locoregional management has, as its goal, a reduction in both distant and locoregional recurrences. However, the results from the Head and Neck Contract Program did not suggest any role of the adjuvant chemotherapy.[15] This study, a three arm trial, compared surgery and postoperative radiation to both neoadjuvant cisplatin and bleomycin and neoadjuvant chemotherapy plus adjuvant cisplatin for 6 months after surgery and radiation. No differences in overall survival between 3 arms were observed, but significant decrease in distant metastases were reported in patients who received chemotherapy. The Head and Neck Intergroup study 0034 came to a similar conclusion.[16] Total of 446 patients were entered in this trial. The 4 years acturial survival rate was 44% in radiotherapy arm and 48% in the chemotherapy arm, with disease free survival rate of 38% and 46% respectively (results not statistically significant). No differences in locoregional recurrence rate or time to recurrence were noted. Once again, an overall reduction in distant metastasis did not reach statistical differences (23% VS 15%, p value = 0.3). In summary, currently there is no role for routine adjuvant chemotherapy. The adjuvant chemotherapy schedules, however, should be considered in situation of high risk for local as well as distant relapse.

III. Concurrent chemotherapy and radiation therapy

The failure of neoadjuvant and adjuvant chemotherapy to improve overall survival stimulates investigators to look for a new strategy of combined treatment. The rational for concurrent chemotherapy and radiotherapy recognizes that both modalities are independently active management. When using together, there is additional potential for synergism. Randomized trials have been conducted using single active agent including

5FU, metrotrexate, bleomycin, hydroxyurea, mitomycin C, cisplatin, and carboplatin simultaneously with radiation. [2,5,7,17,18] No survival benefit was found from this treatment approach, despite a higher overall response rate in chemoradiotherapy patients. The multiagent chemotherapy concomitantly with radiation was next explored. Many pilot trials reported a suggestive but inconclusive benefit for the concurrent management. Keane and associates employed a randomized study to compare the concurrent chemotherapy and standard radiotherapy in patients with locally advanced head and neck carcinoma.[19] In the concurrent chemoradiotherapy arm, patients were received mitomycin C plus 5FU simultaneous with radiation dose of 50 Gy split course. The results of this study shows no survival benefit in combined treatment group. Studies from Yale University[20], Cleveland Clinic[21] also confirm no survival advantage in concurrent arm, despite the locoregional control and disease free survival were significant improved. A number of combination drug therapy programs have been developed including cisplatin plus 5FU, carboplatin plus 5FU, vinblatine plus metrotrexate with or without 5FU, mitomycin C plus 5FU or bleomycin. However, the most attractive regimen used in recent clinical trial is the combination of cisplatin and 5FU. Bolus cisplatin is given at 80-100mg/m^2 plus 5FU 800-1000 mg/m^2 per day intravenous infusion for 4-5 days. The treatment is repeated every 3 weeks. Carboplain, cisplatin derivative, is substituted for cisplatin in some trials because less gastrointestinal and renal toxicity.[22] Few randomized trials have been addressed this treatment strategy. Aldelstein et al[23] and Taylor et al[12] employed a regimen of 5FU and cisplatin which were given sequentialy versus concomitantly with radiotherapy. The results suggested an advantage to simultaneously rather than sequential therapy for relapse free survival but again the overall survival was not significant. The explanation of this result comes from treatment interruption and most published trials were too small to detect any effect on survival. Administering multiple cytotoxic drugs during radiation therapy substantially increase toxicity and often necessitates frequent radiation breaks.[12,18,21-26] The combined treatment produced toxic effects associated with both chemotherapy and radiotherapy. Patients treated with concomitant chemoradiotherapy have more toxicity than patients treated with radiotherapy alone.[12,25,26] The major acute reactions include mucositis and dermatitis. These reactions occurred early in the course of treatment and the mean total time was significantly longer in chemotherapy group compared in radiotherapy alone. Major chemotherapy related toxicity is hematologic toxicity including leukopenia, thrombocytopenia and anemia. It occurred approximately 10-15% of severe hematologic complication, include total leukocyte count less than 3000/mm^3 , platelet count less than 100,000/ mm^3 and hemoglobin level less than 8 gm%, in patients who received

chemoradiotherapy.[24] Moreover, excess of non- cancer death is noted in concomitant treatment in some trials.[12] The most recent and largest meta- analysis of concurrent approach reported by the Meta- analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) Collaborative Group reviewed 63 randomized trials, including 10,741 patients.[27] This meta- analysis updated data on all patients in randomized trial between 1965 and 1993. This included patients with carcinoma of the oropharynx, oral cavity, larynx, and hypopharynx. The first meta- analysis included 63 trials that compared locoregional treatment with or without chemotherapy. There was small but significant benefit for overall survival in favor of chemotherapy with a 10% reduction in the hazard ratio of death (95% CI 6-15% reduction). This reduction corresponds to an absolute benefit of 4%, in both 2 years (from 50 to 54%) and 5 years (from 32 to 36%) survival. Among the combined chemotherapy trials, these were divided according to timing of chemotherapy: neoadjuvant, adjuvant, and concomitant. Neither neoadjuvant nor adjuvant chemotherapy trials produced significant effect on survival. In 26 concomitant trials, there were significant overall benefit of chemotherapy with increasing 5 year absolute survival of 8%. The effect of concurrent chemotherapy was significant greater with multiagent chemotherapy than with single chemotherapy (hazard ratio 0.69 VS 0.87). The successful of such treatment, however, is possible with intensive supporting cares. Close physician follow up, early and appropriate antibiotic usage and aggressive alimentary supporting are necessary.

In summary, although the concomitant chemoradiotherapy approach improve locoregional control as well as absolute survival rate, not all patients are well suited for this management. As mentioned above, the synchronous treatment can cause severe acute toxicity during treatment. A compliant and strongly committed patient is required to complete therapy. The physician experiences and the health care team are also necessary to provide supportive care during treatment.

Conclusion

Advanced in treatment of head and neck cancer reported over a few decades have provided a lot of information. The multidisciplinary management optimize the therapeutic outcome of the patients with locoregional advanced disease. Chemotherapy can be additive or supra- additive interaction with radiation therapy. There was a small but statistically significant benefit on survival when chemotherapy was added to a locoregional treatment in patients with non- metastatic head and neck squamous cell carcinoma. Concomitant chemoradiotherapy shows benefit over other combined chemotherapy managements. This improves locoregional control and enhances disease free survival. Finally, this strategy increases an absolute

survival about 8%. The induction chemotherapy can dramatically reduce the size of tumor. Despite this success, a survival benefit has not been confirmed. Adjuvant chemotherapy schedules provided no survival advantage, despite significant reduction of distant metastatic disease. On the other hand, toxicity related to combined treatment must be regarded throughout. It will be important to evaluate morbidity, quality of life and cost- effectiveness. Future direction will focus on newer chemotherapeutic agent such as taxanes, vinorelbine and gemcitabine, and also radioprotectors as well as unconventional radiation programs.

References

1. Derassme S, Martin N, Sontipong S. Cancer in Thailand vol II, 1992-1994: IARC Technical Report. 34;1999.
2. Clayman GL, Lippmon SM, Laramore GE, Hong WK. Head and Neck Cancer. In: Holland JF, Bast, Jr RC, Morton DL, Frei III E, Kufe DW, Weichselbaum RR , editors. Cancer Medicine. 4th ed. William & Wilkins; 1997. p.1645-799.
3. Dimery IW, Hong WK. Overview of Combined Modality Therapies for Head and Neck Cancer. J Natl Cancer Inst 1993; 85:95-111.
4. Rotman R, Aziz H, Wasserman TH. Chemotherapy and Irradiation. In: Parez AC, Brady LW, editors. Principle and Practice of Radiation Oncology. 3rd ed. Philadelphia: Lippincott - Raven; 1997. p.705-22.
5. Aldelstein DJ. Chemotherapy for Head and Neck Cancer. 41st Annual Scientific Meeting of the American Society for Therapeutic Radiology and Oncology; 1999 Oct 31- Nov 4. San Antonio, Texas;1999.
6. Winter HR, Mc Bride. Biologic Basis of Radiation Therapy. In: Parez AC. Brady LW, editors. Principle and Practice of Radiation Oncology 3rd ed. Philadelphia: Lippincott - Raven; 1997. p.79-118.
7. Schantz SP, Harrison LB, Forastiere AA. Tumor of Nasal Cavity and Paranasal Sinuses, Nasopharynx, Oral cavity and Oropharynx. In: De Vita VT, Hellman S, Rosenberg SA, editors. Cancer: Principle and practice of Oncology. 4th ed. Philadelphia: Lippincot - Raven; 1997. p.741-801.
8. Vokes EE, Schilsky RL, Weichbselbaum RR, Kozloff MF, Panje WR. Induction Chemotherapy with Cisplatin, Fluorouracil, and High Dose leucoverin Rescue for Locally Advanced Head and Neck Cancer: A Clinical and pharmacologic Analysis. J Clin Oncol 1990;8:241-7.
9. Paccagnella A, Orlando A, Marchlori C, Zorat PL, Cavaniglia G, Sileni VC, et al. A Phase III Trial of Initial Chemotherapy in Stage III and IV Head and Neck Cancer: A study by the Grouppo di Studio sui Tumori dell Testa edel Callo. J Natl Cancer Inst 1994;86:265-72.
10. Department of Veterans Affairs Laryngeal Study Group. Induction Chemotherapy Plus Radiation Compared with Advanced Laryngeal Cancer. N Engl J Med 1991; 324:1685-93.

11. Lefebvre JL, Chevalier D, Luboinski, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in Pyriform Sinus cancer: Preliminary Results of a European Organization for Research and Treatment of Cancer Phase III Trial. J Natl Cancer Inst 1996;88:890-99.
12. Taylor SG IV, Murthy AK, Vannetzel JM, Colin P, Dray M, Calarell DD, et al. Randomized Comparison of Neoadjuvant Cisplatin and Fuorouracil Infusion Followed by Radiation Versus Concomitant in Advanced Head and Neck Cancer. J Clin Oncol 1994;12:385-95.
13. Griem KL, Murthy AK, Vannetzel JM. The Five Year Results of a Randomized Trial of Sequential Versus Concomitant Cisplatin and Florouracil and Radiation in Advanced Head and Neck Cancer. Int J Radiat Oncol Biol Phys 1995;32 (supple): 194-7.
14. Forastiere AA. Larynx preservation trials: A Critical Appraisal. Sem Radiat Oncol 1998;8:254-61.
15. Jacobs C and Makach R. Efficacy of Adjuvant Chemotherapy for Patients with Resectable Head and Neck Cancer: A Subset Analysis of the Head and neck Contract Program. J Clin Oncol 1990;8:838-47.
16. Laramore G, Scott C, Al- Sarraf M. Adjuvant Chemotherapy for Resectable Squamous Cell Carcinomas of Head and Neck: Report on Intergroup Study 0034. Int J Radiat Oncol Biol Phys 1992;23: 705-11.
17. Fu KK, Phillips TL, Siverberg IJ. Combined Radiotherapy and Chemotherapy with Bleomycin and Metrotrexate for Advanced Inoperable Head and Neck Cancer: Update of a Northern California Oncology Group Randomzied Trial. J Clin Oncol 1987;5: 1410-8.
18. Brownman GP, Cripps C, Hodson DI. Placebo- Controlled Randomized Trial of Infusion Fluorouracil During Standard Radiotherapy in Locally Advanced Head and Neck Cancer. J Clin Oncol 1994;12: 2684-93.
19. Keane TJ, Cummings BJ, O'Sullivan B. A Randomized Trial of Radiation therapy Combined with Mitomycin C and 5 Fluorouracil as Initial Treatment for Advanced Laryngeal and Hypopharyngeal Squamous Carcinoma. Int J Radiat Oncol Biol Phys 1993;25:613-9.
20. Haffty BG, Son YH, Papac R. Chemothrerapy as an Adjuvant to Radiation in the Treatment of Squamous Cell Carcinoma of Head and Neck: Results of the Yale Randomized Trial. J Clin Oncol 1997;15:268-76.
21. Aldelstein DJ, Saxton JP, Lavertu P. A Phase III Randomized Trial Comparing Concurrent Chemotherapy and Radiotherapy in Resectable Stage III and IV Squamous Cell Head and Neck Cancer: Preliminary Results. Head Neck 1997;19:567-75.
22. Calais G, Alfonsi M, Bardet E, Sire C, Bourgeois H, Bergerot C, et al. Randomized Study Comparing Radiation Alone (RT) Versus Concomitant Chemotherapy

(CT) in Stage III and IV Oropharynx Carcinoma (ASCORO). Preliminary Results of the 94.01 Study from The French Group of Radiation Oncology for Head and Neck Cancer (GORTEC). Proc ASCO 17th 1998.

23. Aldelstein DJ, Sharan VM, Earle S. Simultaneous Versus Sequential Combined Technique Therapy for Squamous Cell Head and neck Cancer. Cancer 1990;65:1685-94.
24. Merlano M, Vitale V, Rosso R. Treatment of Advanced Squamous Cell Carcinoma of the Head and Neck with Alternating Chemotherapy and Radiotherapy. N Engl J of Med 1992;327:1115-21.
25. Merlano M, Benassa M, Corvo R, Rosso R, Vitale V, Blengio F, et al. Five Year Update of a Randomized Trial of Alternating Radiotherapy and Chemotherapy Compared with Radiotherapy Alone in Treatment of Unresectable Squamous Cell Carcinoma of the Head and Neck. J Natl Cancer Inst 1996;88:583-9.
26. Brizel DM. Radiotherapy and Concurrent Chemotherapy for the Treatment of Locally Advanced Head and neck Squamous Cell carcinoma. Sem Radiation Oncol 1998;8:237-46.
27. Pignon JP, Bourhis J, Domenge C. Chemotherapy Added to Locoregional Treatment for Head and Neck Squamous Cell carcinoma: Three Meta- analyses of Updated.

Individual Data. Meta-analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) collaborative Group. Lancet 2000; 18:949-55.

บทบาทของยาเคมีบำบัดในการรักษามะเร็งบริเวณศีรษะและลำคอระยะลุกลามเฉพาะที่

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บทคัดย่อ

มะเร็งบริเวณศีรษะและลำคอ เป็นมะเร็งที่พบบ่อยในประเทศไทย[1] การรักษามาตรฐานประกอบด้วยการผ่าตัด การใช้รังสีรักษาหรือทั้งสองชนิดร่วมกัน อย่างไรก็ตาม ผลของการรักษายังไม่เป็นที่น่าพึงพอใจโดยเฉพาะเมื่อโรคอยู่ในระยะที่มีการลุกลามเฉพาะที่ นอกจากนี้การรักษามะเร็งยังต้องคำนึงถึงการทำงานและรูปทรงของอวัยวะบริเวณศีรษะและลำคออีกด้วย เพื่อให้ผู้ป่วยมีคุณภาพชีวิตที่ดีระดับหนึ่งภายหลังจากการรักษา ในปัจจุบันได้มีการนำยาเคมีบำบัดมาใช้ในการรักษามะเร็งบริเวณศีรษะและลำคอ ทั้งนี้เพื่อเพิ่มผลของการรักษาและเพิ่มโอกาสในการรักษาแบบสงวนอวัยวะไว้ บทความนี้เป็นการสรุปวิวัฒนาการและประโยชน์ของการนำยาเคมีบำบัดมาใช้ในการรักษามะเร็งบริเวณศีรษะและลำคอระยะลุกลามเฉพาะที่

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