はじめに

切除不能もしくは局所進行の頭頸部がんに対する標準治療はcisplatin（CDDP: 100 mg/m^2, day 1, 22, 43）を放射線治療（radiation therapy: RT）と併用する化学放射線療法である[1-3]。海外においてCDDP（100 mg/m^2, day 1, 22, 43）＋RT療法は全身状態や臓器機能が良好な患者に行われており，一般臨床では低用量CDDP（30～40 mg/m^2）毎週投与を放射線治療と併用するweekly CDDP＋RT療法[4,5]，もしくは放射線治療と併用し3週間ごとにCDDP 20 mg/m^{2}を4日間連日投与する3-weekly CDDP分割＋RT療法（20 mg/m^2/day, day 1～4, 22～25, 43～46）が実臨床で用いられている。ニューロキニン（NK$_1$）受容体拮抗薬であるアプレピタント（aprepitant: APR）は，国内外における各種ガイドラインにおいて高度催吐性リスクの抗がん薬への3日間内服（1日目125 mg, 2・3日目80 mg）が推奨されている予防的制吐薬である[6-8]が，National Comprehensive Cancer Network（NCCN）ガイドラインでは，CDDP投与量が50 mg/m^{2}未満の場合は中等度催吐性リスクに分類され[9,10]，アプレピタントの使用は推奨されていない（表1）。われわれはアプレピタントが本邦で承認を受け，院内採用となった2010年ごろより，アプレピタントを3-weekly CDDP分割＋RT療法において予防内服として図1のように使用していたが，各種ガイドラインを考慮し，2011年7月よりCDDP初回投与に際してはアプレピタントを使用せず，Grade 2以上の悪心が発現し，かつ医師・薬剤師が必要と判断した場合にのみアプレピタントを使用した。本調査は3-weekly CDDP分割＋RT療法における悪心・嘔吐に対するアプレピタントの予防的効果を検証した初めての報告である。

表1 国内外ガイドラインで推奨されている3-weekly CDDP分割＋RT療法における予防的制吐薬

Doses/Guidelines	ASCO	NCCN	MASCC	JSCO
≧50 mg/m^2	High	High	High	High
<50 mg/m^2		Moderate		
Multiple-day	High	Not classified	Moderate	High

⬇

Emetic risk	Acute			Delayed	
High	5-HT$_3$RA	DEX	APR	DEX	APR
Moderate	5-HT$_3$RA	DEX		DEX	

5-HT$_3$RA: 5-HT$_3$ receptor antagonist,
DEX: dexamethasone, APR: aprepitant
ASCO: American Society of Clinical Oncology
NCCN: National Comprehensive Cancer Network
MASCC: Multinational Association of Supportive Care in Cancer
JSCO: Japan Society of Clinical Oncology

Ⅰ．対象と方法

1．対　象

国立がん研究センター東病院において3-weekly CDDP分割＋RT療法を受けた頭頸部がん患者のうち，2010年1月～2010年6月までの期間でアプレピタントを使用していた23症例をA群，2011年7月～2011年12月までの期間でアプレピタントを使用していない34症例をB群とした。

2．方　法

本研究は診療録を基にこれら2群における，①悪心のGrade，②嘔吐頻度，③悪心が化学放射線療法に与えた影響について後ろ向きに調査し，比較した。悪心はNational Cancer Institute-Common Terminology Criteria Adverse Events ver3.0（NCI-CTCAE v3.0）を用いて評価し，3-weekly CDDP分割＋RT療法中における最も高いGradeを抽出した。

なお，本研究は「疫学研究に関する倫理指針」を遵守し，国立がん研究センター倫理審査の手続きに従い許可されたものであり，対象患者の倫理性は担保されている［研究課題番号（2012-017）］。

3．調査項目

統計解析には，頻度の比較にχ^2検定もしくはFisher's直接確率計算法を用い，$p<0.05$の場合に有意差ありとした。

Ⅱ．結　果

1．患者背景（表2）

年齢中央値はA群60（35～73）歳，B群62（31～71）歳，男女比（男性/女性）はA群（18/5），B群（30/4），PS 0/1はA群（20/3），B群（31/3）であり，両群間に差はなかった。

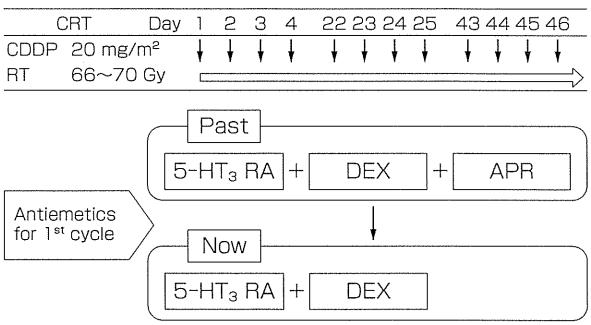

図1 3-weekly CDDP分割＋RT療法のレジメン内容と当院で使用された予防的制吐薬
5-HT$_3$RA: 5-HT$_3$ receptor antagonist
DEX: dexamethason, APR: aprepitant

表2　患者背景

調査項目		A群 (n=23)	B群 (n=34)
Gender	Male/Female	18/5	30/4
Age (years)	Median (range)	60 (35～73)	62 (31～71)
PS	0/1	20/3	31/3
5-HT_3 RA	G/P*	21/2	34/0
IC**	Yes/No	18/5	14/20

*G: granisetron　P: palonosetron
**IC: induction chemotherapy
PS: Eastern Cooperative Oncology Group performance status

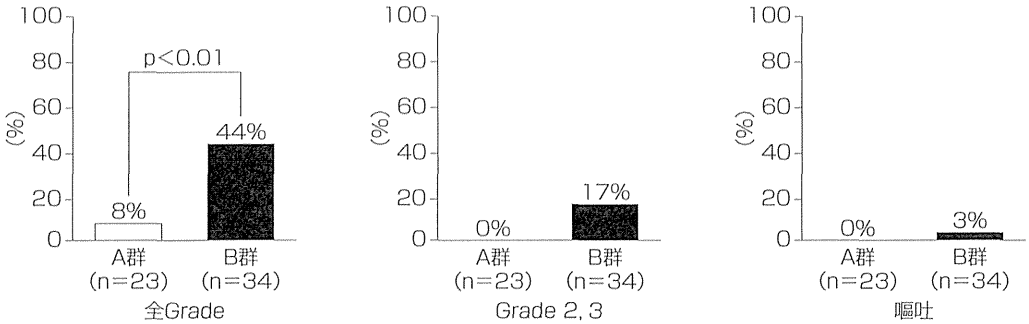

図2　3-weekly CDDP分割＋RT療法におけるCTCAE v3.0による悪心の最大Gradeと嘔吐の頻度

2．悪心の最大Grade（図2）

発現した悪心の最大Grade (0/1/2) はA群 (21/2/0)，B群 (19/9/6) であった。悪心が発現した頻度はA群8% (2/23)，B群44% (15/34) であり，A群で有意に低かった（$p<0.01$）。1コース目にGrade 2の悪心を呈したB群の6症例のうち5症例に次コース，アプレピタントが追加処方され，60% (3/5) の症例で悪心が軽減した。

また，Grade 2の悪心を呈したB群の6例のうち，悪心の発現のタイミングは急性期（24時間以内）1例 (17%)，遅発性期が5例 (83%) であった。

3．嘔吐の頻度（図2）

発現した嘔吐はA群0例 (0%)，B群1例 (3%) であった。嘔吐を認めたB群の1例は遅発期での発現であった。

4．悪心による治療への影響（表3）

3-weekly CDDP分割＋RT療法において，悪心を理由としてCDDP減量もしくは放射線の照射休止・中止する症例はなかった。CDDP減量はA群において16例 (70%) あり，B群は16例 (47%) であった。その理由としてはA群，B群ともに全例が腎機能低下であった。

表3　3-weekly CDDP分割＋RT療法の投与休止・中断およびCDDP減量の内訳

	理由	A群 (n=23)	B群 (n=34)
投与量減量	腎機能低下	16	16
投与中止	発熱	3	0
	貧血	2	0
	腎機能低下	1	0
	肺炎	1	0
	せん妄	0	1
	吃逆	0	1
	患者希望	0	1
	その他	5	3

Ⅲ．考　察

アプレピタントは悪心・嘔吐を改善し，化学療法を受けるがん患者のQOLを改善することが報告されている[11-13]薬剤である。アプレピタントの併用はCDDPを50 mg/m^{2}以上用いる高度催吐性リスクの化学療法に推奨され，そのエビデンスは確立しているが，低用量のCDDP療法施行時に関してはその有用性は明確ではない。われわれは，20 mg/m^2/dayの低用量CDDPを4日間連続で用いる3-weekly CDDP分割＋RT療法においてアプレピタント使用時，未使用時の悪心の有無を比較調査した。その結果，全体として悪心が50%，そしてGrade 2以上の悪心が20%であったが，アプレピタントを併用することで悪心が有意に改善されることを明らかにした。また，アプレピタントを併用していないB群において制御できない悪心であると医師に判断され，予防的にアプレピタントを追加使用した症例においては悪心が改善したことから，アプレピタントを3-weekly

CDDP分割＋RT療法において使用することは有用であるといえる。本調査において，悪心・嘔吐がCDDPの減量もしくは放射線治療の休止・完遂に影響を及ぼすことはなかったが，悪心・嘔吐は抗がん薬の副作用のなかで患者にとって最もつらい症状であり[14]，持続すると低栄養，脱水，電解質異常につながることから，患者のQOLを維持しつつ治療を継続するためには悪心・嘔吐のコントロールは必須である。特に，頭頸部がんにおける化学放射線療法は疾患の根治をめざしていることから治療の完遂が最終目標であり，付随する悪心への対応が重要であるため適切な支持療法の選択が求められる。なお，本調査における症例は主に男性であったが，男女間における悪心の差はみられなかった。また，表2に示すように本調査はA群の2例を除き5-HT_3拮抗薬としてグラニセトロンが使用されており，この結果はパロノセトロンを使用した際のデータではない。遅発性期の悪心・嘔吐に対してより半減期の長いパロノセトロンを用いることで遅発性の悪心・嘔吐制御の成績が向上する可能性もあることから，今後はアプレピタント＋グラニセトロン＋デキサメタゾン群に対するパロノセトロン＋デキサメタゾン群の比較試験が考慮される。アプレピタントは有用な予防的制吐薬であるが薬剤相互作用のある薬剤であるために効果の持続があり，遅発性期に効果があるパロノセトロンはアプレピタントが使用できない場合やアプレピタントにより制御できない悪心をカバーできる可能性がある。高度催吐性リスクの化学療法に対する臨床試験は多数行われているが，本調査のような分割による連日投与の化学療法においてデータが少ないことから，これらのような今後の検証が必要である。アプレピタントをはじめ新規の制吐薬が使用可能になってきていることから，実臨床においては各種ガイドラインおよび臨床試験の報告を踏まえた支持療法薬の選択と，前向きの臨床試験によるさらなる検証が求められる。

本研究は第10回日本臨床腫瘍学会にて報告した。なお，著者は申告すべき利益相反を有しない。

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JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2014, 1–9
doi: 10.1093/jjco/hyu209
Review Article

OXFORD

Review Article

Definitive radiotherapy for head and neck squamous cell carcinoma: update and perspectives on the basis of EBM

Takeshi Kodaira[1,*], Yasumasa Nishimura[2], Yoshikazu Kagami[3], Yoshinori Ito[4], Naoto Shikama[5], Satoshi Ishikura[6], and Masahiro Hiraoka[7]

[1]Department of Radiation Oncology, Aichi Cancer Center Hospital, Aichi, [2]Department of Radiation Oncology, Kinki University Faculty of Medicine, Osaka, [3]Department of Radiology, Showa University School of Medicine, Tokyo, [4]Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, [5]Department of Radiation Oncology, Saitama Medical University International Medical Center, Saitama, [6]Department of Radiology, Koshigaya Municipal Hospital, Saitama, and [7]Department of Radiation Oncology and Image-Applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan

*For reprints and all correspondence: Takeshi Kodaira. E-mail: 109103@aichi-cc.jp

Received 29 October 2014; Accepted 19 November 2014

Abstract

Radiotherapy plays an essential role in the management of head and neck squamous cell carcinoma. Radiotherapy has a distinct advantage over surgical procedures in that it could achieve organ and function preservation with an efficacy similar to that of surgical series. To improve the clinical outcomes achievable by radiotherapy, altered fractionated radiotherapy has been prospectively tested for early and intermediate risk diseases, and was previously shown to be beneficial for local control and survival. Radiotherapy alone is insufficient for locally advanced disease; therefore, concurrent chemoradiotherapy is typically performed and plays an important role. A meta-analysis (Level Ia) revealed that the concurrent use of platinum agents appeared to improve tumor control and survival; however, this was accompanied by increases in the rates of both acute and late toxicities. Regarding radiation techniques, intensity modulated radiotherapy evolved in the 1990s, and has been globally used to treat head and neck squamous cell carcinoma patients. Intensity modulated radiotherapy reduces the exposure of normal tissue to radiation while preserving excellent dose coverage to the target volume; therefore, the rate of late toxicities especially xerostomia is minimized. Small size randomized studies and a meta-analysis have provided evidence to support the benefits of intensity modulated radiotherapy over two-dimensional or three-dimensional radiation therapy. Intensity modulated radiotherapy can also preserve quality of life following definitive chemoradiotherapy. Further improvements using intensity modulated proton therapy are warranted.

Key words: intensity modulated radiotherapy, chemoradiotherapy, altered fractionated radiotherapy

Introduction

Radiotherapy (RT) for head and neck squamous cell carcinoma (HNSCC) plays an important role in the preservation of organs and their functions. Small volume tumors, such as those of the T1–2 category, are expected to achieve 70–90% local control with RT (1–4); however, the efficacy of RT alone was shown to be reduced in cases of T3–4 category tumors (5–7). Controversy still surrounds the ability of RT to achieve tumor control and larynx preservation in locally advanced laryngeal and hypopharyngeal cancers. Although concurrent chemoradiotherapy (CCRT) appears to be the mainstay for successful

larynx preservation compared with surgery, increases in late morbidity and controversy in survival benefit with a longer follow-up are serious issues(8,9). Intensity modulated radiotherapy (IMRT) has rapidly evolved in the past two decades, and is considered the standard care of definitive RT for HNSCC (10). Previous studies reported that the rate of late morbidities especially xerostomia appeared to be lower following IMRT (11–16), and improved quality of life (QOL) after RT could be expected (17–20). Thus, the adaptation of IMRT for CCRT represents a reasonable combination to minimize the risk of the associated toxicities. Multi-agent induction chemotherapy containing taxanes and bioradiotherapy has been extensively researched in an attempt to balance treatment efficacy and safety (21–23).

Early stage

Optimal fractionation schedule

Prolonging the duration of RT for HNSCC is known to have a distinct negative impact on clinical outcomes (24–26), and has been attributed to a biological phenomenon, the so-called accelerated repopulation, which is accompanied by the development of radioresistance by tumor cells (27). To improve clinical outcomes, an altered fractionation (AF) schedule that minimizes the treatment duration, has been clinically tested on patients with low and intermediate risk diseases (28–31). A meta-analysis revealed that AF improved both local control and survival over those achieved by the standard fractionated schedule (32).

Early glottis cancer is considered to be an optimal model for presenting the advantages of AF. Definitive RT was previously reported to have acquired sufficient survival outcomes with excellent local control for patients with this cancer, even if salvage surgery for local recurrence was needed. Patients with T1–2N0 glottic cancer typically receive 66–70 Gy over 6.5 weeks on an outpatient basis. AF is expected to improve tumor control, thereby reducing the burden on patients and working staff, and ameliorating the cost of treatment for public insurance. Several retrospective studies have demonstrated the advantages of AF radiotherapy (>2.0 Gy per fraction) for glottis cancer (33,34); however, few prospective studies have been conducted in a multi-institutional setting (Table 1) (29–31). Yamazaki et al. (29) reported that the AF arm in a randomized controlled study from a single institute showed a significant advantage for local control. A total of 180 patients with T1 glottic tumors were entered into this trial; the AF arm ($N = 91$) received 56.25–63 Gy over 5–5.5 weeks with a 2.25 Gy fraction, while the SF arm received 60–66 Gy over 6–6.5 weeks with a 2 Gy fraction. The 5-year local control rate of the AF arm was significantly better than that of the standard fractionation (SF) arm (92 vs. 77% $P = 0.004$). Moon et al. (30) reported the findings of multi-institutional randomized controlled trial (RCT) for T1–2N0M0 glottic cancer. However, this trial was stopped due to poor accrual, because only 156 patients were ultimately registered against the planned 282 patients. The AF arm of 63–67.5 Gy with a 2.25 Gy fraction achieved slightly better local control than that of the SF arm of 66–70 Gy with a 2 Gy (93 vs. 76%; $P = 0.056$). The Radiation Therapy Study Group of the Japan Clinical Oncology Group (JCOG) conducted a multi-institutional RCT trial of the JCOG 0701 to demonstrate the non-inferiority of the efficacy of the AF arm with 2.4 Gy per fraction over the SF arm with 2 Gy per fraction (31). A total of 370 patients were registered in this study until January 2013, and a follow-up will be conducted on January 2016. It is the first multi-institutional RCT trial to investigate the advantage of AF radiotherapy for early glottic cancer, the findings of which are highly anticipated.

Intensity modulated radiotherapy

The incidence of oropharyngeal cancer (OPC) is gradually increasing, while that of human papilloma virus (HPV) infection is also high (35,36). Patients with OPC-related HPV infection have a favorable prognosis (37–39), and radiotherapy plays an important role among the treatment modalities available for these patients. The adaptation of IMRT could reduce the rate of late toxicity especially xerostomia; thus, it is considered a standard method in definitive RT for OPC (40,41). Several RCT have been conducted to demonstrate the advantages of IMRT for HNSCC patients including OPC (11,13). The RTOG 00-22 trial is a prospective single arm trial that tested the efficacy of IMRT using a slightly hypofractionated schedule with 2.2 Gy per fraction for early OPC patients with T1–2N0–1M0 diseases (42). The 2-year survival rate was reported to be 95.5%, with a loco-regional failure rate of only 9%. The 1- and 2-year rates of Grade 2 xerostomia were 25 and 16%, respectively. To further improve QOL, unilateral neck irradiation using IMRT for OPC, with a favorable prognostic factor, is expected to represent an attractive treatment option (43). Al-Mamgani et al. (44) retrospectively evaluated unilateral neck IMRT for early disease in this category in a relatively large series ($N = 185$). The 5-year local control rate was reported to be 91% with 7% Grade 2 xerostomia. Although this was a retrospective

Table 1. Reported series of definitive radiotherapy with altered fractionation for early glottic cancer

Author	Material	Number	Style	Total dose (Gy)	Fraction size (Gy)	LC (%)	OS (%)	Complication rate G3 or more
Robertson (33)	T1–4	118	Retrospective	60	2	55–70/39–62	NR	NR
		15		56.5	2.26	80/	NR	NR
		111		60	2.4	95/75	NR	NR
		37		54	3	81/37	NR	NR
		22		51	3.4	85/40	NR	NR
van der Voet (34)	T1	64	Retrospective	60–66	2	83–85		NR
		79		60, 61.6	2.4, 2.8	90–93		1.8–3.1
		142		62, 65	3.1, 3.25	93		10.9–12.5
Mendenhall (1)	T1–2	304	Retrospective	56.25/63 (T1/2)	2.25	93/75	NR	1.6
Yamazaki (29)	T1	180	Prospective Phase III	56.25/63 (S/L)	2.25	92	87	0
Moon (30)	T1–2	156	Prospective Phase III		2.25	88.5(LPFS)	86.6	0
RTOG 9512 (28)	T2	250	Prospective Phase III	79.6	1.2 bid	78	72	8.5
JCOG 0701 (31)	T1–2	370	Prospective Phase III	60/64.8 (T1/T2)	2.4			

S, small size; L, large size, bid, twice-a-day, LC, local control; LPFS, larynx progression-free survival; OS, overall survival; NR, not reported.

study, limited field IMRT was expected to successfully achieve high local control with a low incidence of xerostomia. The JCOG Radiation Therapy Study Group has now conducted the JCOG 1208 study to test the efficacy of IMRT using a limited target volume (TV) for patients with OPC of the T1–2N0–1 category. In this protocol, contralateral Level II–III area was excluded from prophylactic TV in the case of patients with tonsillar cancer. And only ipsilateral Level IV area was included in TV for patients with N1. This is the first multi-institutional prospective trial using this modified TV for early OPC.

Locally advanced stage

The efficacy of RT alone for locally advanced (LA) disease is lower than that of surgical series. The administration of cytotoxic agents to improve disease control has been practically considered for patients with certain medical conditions (5,23,45–47). CCRT was reported to significantly improve both disease control and survival in several RCTs, and these findings were also supported by meta-analyses (5,45,46,48). RT accompanied with platinum agents is considered the standard treatment for LA-HNSCC (45).

RT with cetuximab [CET; anti-epidermal growth factor receptor (EGFR)] also improved overall survival (OS) and LC over those with RT alone (47,49). In the Bonner trial, Stage III–IV patients were randomly assigned to a bioradiotherapy (BRT) arm or RT arm. The BRT arm showed significant improvements in loco-regional control and OS [hazard ratio (HR) 0.68; $P = 0.005$; HR = 0.74 $P = 0.03$]. No significant difference was observed in the rate of acute toxicities between both arms. Therefore, it is important to note that a direct comparison has not yet been conducted between the results achieved by BRT and CCRT, which is considered the standard treatment for LA-HNSCC (50).

AF has also been shown to increase local control for LA-HNSCC in several RCTs. A meta-analysis of 15 trials with 6515 patients revealed that AF was significantly advantageous for local control and OS (Level Ia) (32). The majority of cohorts were comprised of OPC patients (47.2%) and Stage III patients, who were expected to have relatively good prognoses, and these groups had slightly better OS in the subset analysis.

Although both chemical modulations by CCRT or BRT and dose modifications by AF increase tumor control, they are also accompanied by increased rates of acute and late toxicities due to definitive RT. The adaptation of IMRT should minimize the rates of these toxicities and, as such, is highly recommend for use in an intensive strategy for LA-HNSCC (13,16,20).

Optimal method of chemotherapy

The standard treatment for locally advanced HNSCC still remains concurrent chemoradiotherapy (CCRT) with cisplatin (45). Previous studies reported Level Ia evidence for the efficacy of CCRT (46,48).

MACH-NC trial comprised 93 trials with 17 346 patients, conducted between 1965 and 2000, revealed that the efficacy of CCRT was higher than that of induction or adjuvant chemotherapy (46). The administration of chemotherapy showed a 4.5% absolute benefit in survival and reduced the HR by 12% ($P < 0.0001$). Regarding the timing of chemotherapy, CCRT achieved a 6.5% absolute benefit in 5-year OS, and a 19% reduction in the HR of OS. In that study, induction chemotherapy (IC) led to moderate benefits in OS and had an apparent advantage by decreasing the rate of distant metastasis (46). This study also showed the benefits of CCRT were less in elderly patients ($P = 0.003$).

IC with taxanes containing multi-agents (ITM) was recently reported to be more advantageous for OS and disease control than cisplatin and 5-FU (PF) in RCTs (21,22), and these findings were confirmed by a meta-analysis (23). Several RCTs were previously conducted to compare the efficacy of ITM to that of PF; however, its apparent benefits over that of immediate CCRT have not been reported until now (51–53). One of the weaknesses of the ITM strategy was the significant increase in treatment-induced toxicities, which decreased compliance of following CCRT (54). Approximately half of the ITM cohorts could not receive chemotherapy during radiotherapy (21,22), which may have decreased the efficacy of CCRT. Several studies attempted to test ITM followed by BRT (55,56). In the Bonner trial, RT with CET was reported to induce similar acute toxicities to those of RT alone (49). ITM followed by BRT represents an attractive strategy for managing treatment toxicities without sacrificing efficacy. Ghi et al. (56) performed a randomized Phase II/III trial to test the efficacy of adding IC containing docetaxel, cisplatin and 5-FU. This trial had a 2 × 2 factorial design, in which second randomization of the CCRT arm or BRT arm occurred after first randomization of IC. They reported survival benefits in the ITM arm. Further modifications and optimization are required to balance the efficacies and morbidities of such intensive multidisciplinary treatments.

Role of bioradiotherapy

The Bonner trial reported the significant advantage of BRT toward RT alone in RCT with LA-HNSCC patients (47,49). Only one RCT has demonstrated the benefit of BRT; however, the control arm in this RCT was RT alone, which is not considered a standard treatment for LA-HNSCC. One of the expected merits of BRT is reduced toxicity. In the Bonner trial, acute toxicities were similar between the BRT arm and RT arm. Several randomized Phase II studies compared BRT with CCRT (55,56). The TREMPLIN trial was conducted to test larynx preservation rate of BRT compared with CCRT for patients treated with ITM for LA-HNSCC (55). Local control could not be achieved by 12 patients (21%) in the BRT arm and eight patients (13%) in the CCRT arm; however, this difference was not significant. BRT was shown to have superior compliance over CCRT (71 vs. 43%), and salvage surgery could be performed in six out of nine patients assessed as feasible for surgery in the BRT arm, but in none of the eight patients in the CCRT arm. Consequently, OS rates were similar in both arms. Ghi et al. (56) also conducted a Phase II/III study of randomization of BRT and CCRT arms. This trial also determined the efficacy of ITM with a 2 × 2 factorial design. No significant differences were observed in progression-free survival (PFS) or OS rates between the BRT and CCRT arms.

A systemic review was conducted on 15 trials comprising 1808 patients to compare BRT and CCRT (50). Only three trials were prospective, while the other 12 were retrospective. In this systemic review, CCRT achieved significantly better OS, PFS and LRR than BRT. RTOG 1016, a Phase III trial of BRT versus CCRT for HPV-associated OPC, is currently being conducted (57). This is the first trial to directly compare BRT and CCRT for a favorable risk group. The effectiveness and toxicity of BRT may be demonstrated in this trial, and its findings could also resolve the question as to whether the efficacy of BRT is similar to that of CCRT.

RTOG 0522 trial was designed to compare the CCRT with cetuximab (CET) arm to the CCRT arm (58). The 3-year OS, PFS and loco-regional relapse-free rate (LRF) were similar in both arms; however, the incidence of acute adverse events was higher in the combined arm. These findings suggest that CCRT with anti-EGFR should be tested in clinical trials, and special care should be taken for its clinical use.

To minimize the toxicity of definitive intensive RT, dose reductions using BRT for a favorable group is now being prospectively evaluated

(59). HPV-associated OPC patients are the main target in this trial. Reductions in toxicity are warranted after confirmation of its efficacy in the de-escalation trial.

Larynx preservation

Locally advanced laryngeal (LC) and hypopharyngeal cancers (HPC) have been treated with surgery, while laryngeal preservation (LP) with the aim of preserving the voice and swallowing function without sacrificing survival is considered a reasonable option in clinical practice (Table 2) (5–7,22,60–62). In the 1990s, several RCTs demonstrated the feasibility of the LP strategy (5–7,62,63). Two RCTs compared IC followed by RT with immediate surgery, the Veterans Affairs Laryngeal Cancer Study Group (VALCSG) trial for LC (7) and EORTC 24851 trial for HPC (6). The VALCSG study registered 322 patients with Stage III/IVLC. The IC group received two cycles of 5FU and cisplatin, then responders to chemotherapy were treated with definitive RT. Otherwise patients underwent laryngectomy with or without post-operative RT. In the IC arm, 107 patients (64%) preserved their larynx. The 2-year OS rate of both groups was 68%. In a subgroup analysis, 56% of patients with T4 category tumors and 29% of those with smaller lesions required salvage surgery. In the EORTC 24851 study, 194 patients with T2–4, N0–2b LA-HPC were randomized to an IC arm or immediate surgery arm (6). The DFS rates at 3 and 5 years were 43%/25% for the IC arm and 32%/27% for the surgery arm, respectively. The 3- and 5-year functional LP rates were 64 and 58% for patients with completed treatments from the IC arms. Responses to the LP protocol markedly varied according to the T category (T2 for 82%, T3 for 48% and T4 for 0%). In these two studies, approximately two-thirds of the IC group could preserve the larynxes without sacrificing survival against the surgical series.

RTOG 91-11 study was a RCT conducted to demonstrate the efficacy of three different RT arms including RT alone, IC followed by RT (identical to the VALCSG trial) and CCRT (5,62). A total of 547 patients with Stage III/IV LC were registered in this trial. Its findings were initially reported in 2003 (5), and then updated in 2012 (62). The rates of LP at a median follow-up of 3.8 years and 10.8 years were 83.6 and 81.7% for the CCRT arm, respectively, and were significantly higher than those from the other two arms (70.8 and 67.5% for the IC arm and 65.8 and 63.8% for the RT alone arm). The OS rates at 5 and 10 years did not differ among the treatment groups (55 and 27.5% for the CCRT arm, 59 and 39% for the IC arm and 54 and 31.5% for the RT alone arm). Although failure to achieve local control was lower in the CCRT arm, the rate of toxicity would have considerably increased with a longer follow-up. In this update series, the CCRT arm had better disease control and a higher rate of late toxicity. From the viewpoint of LP, ITM is expected to allow for feasible options, balancing its efficacy and lower toxicity. A multi-institutional consensus panel published guidelines for the conduct of RCTs for LP (64). They recommended the enrollment of patients with T2 or T3 LC or HPC. They also emphasized that clinical and instrumental assessments were essential, and also proposed the endpoint of disease free with a functional larynx, such as *laryngo-esophageal dysfunction-free survival*. Minimum invasive surgery has recently evolved, and objective and functional estimations are needed for comparisons between different treatment modalities including surgical series (60,65).

Role of intensity modulated radiotherapy

The use of IMRT has recently become more widespread, and this modality was supported by novel technological developments in the 1990s (10). Using this technique, conformal dose distributions to the clinical target volume could be achieved with identical dose reductions to the surrounding normal tissue. Several RCTs demonstrated that IMRT could reduce the rate of G2 xerostomia below that of the 2D or 3D technique (Table 3) (11–16). Two East-Asian RCTs were conducted using a small cohort ($N = 45$–56) of early nasopharyngeal

Table 2. Larynx preservation trials using induction chemotherapy for laryngeal and hypopharyngeal cancer

Study	Number	Site	Stage	IC	RT	LP (%)	OS (%)	Larynx toxicity %
VALCSG (7)	332	LC	III–IV	FP	RT	64	68	NR
EORTC24891 (6)	202	HPC	II–IV	FP	RT	22@5 years	38@5 years	NR
RTOG91-11 (62)	547	LC	III–IV	FP	RT/CRT	71/84@5 years	59/55@5 years	6–10/6–17
GORTEC2000-01 (60)	213	LC and HPC	III–IV	FP/TPF	RT	57/70@3 years	60/60@3 years	13.6/6.2
GETTEC (63)	68	LC	II–IV	FP	RT	42	69@2 years	NR
Posner (22)	166	LC and HPC	III–IV	FP/TPF	CRT	32/52@3 years	40/57@3 years	NR
TREMPLIN (55)	153	LC and HPC	III–IV	TPF	CRT/BRT	93/96@3 months	85/86@1.5 years	8.6/9
Prades (61)	71	HPC	III–IV	FP	RT/CRT	68/92@2 years	36/41@2 years	NR

VALCSG, Veterans Affairs Laryngeal Cancer Study Group; LC, laryngeal cancer; HPC, hypopharyngeal cancer; IC, induction chemotherapy; FP, 5FU and ccisplatin, TPF, docetaxel, 5FU and cisplatin, RT, radiotherapy; CRT, chemoradiotherapy; BRT, bioradiotherapy; LP, laryngeal preservation; NR, note reported.

Table 3. Reported series of randomized control trial comparing IMRT to conventional radiotherapy for head and neck carcinoma

Author	Site	Number	Control	Stage I/II (%)	Chemoradiotherapy	6 months–1 year xerostomia IMRT	6 months–1 year xerostomia conv.	LC (%)	OS (%)
Pow (12)	NPC	45	2D	100	No				
Kam (14)	NPC	54	2D	100	No	39.3	82.1		
Nutting (13)	H&N	94	2D	24	Yes	15	74	NS	NS
Gupta (11)	H&N	60	3D	20	Yes	28.8	76	NS	NS
Peng (15)	NPC	616	2D	31	Yes	28.1	57.4	F	F

NPC, nasopharyngeal carcinoma; H&N, head and neck carcinoma; 2D, two dimensional; 3D, three dimensional; IMRT, intensity modulated radiotherapy; conv., conventional radiotherapy; LC, local control; NS, not significantly different; F, IMRT group is favorable.

cancer (NPC) patients, and the findings obtained revealed that xerostomia was subjectively and/or objectively lower in the IMRT arm than in the 2D RT arm (12,14). Nutting et al. (13) reported the findings of a multi-institutional RCT that compared IMRT with 2D RT for OPC and HPC patients. The xerostomia rates at 1 and 2 years were significantly lower in the IMRT group (38 and 29%) than in the 2D RT group (74 and 83%). OS and loco-regional relapse-free survival LRPFS in both groups were not significantly different between both arms. These findings were also supported by a systematic review (16) (Level Ia). Marta et al. (16) conducted a meta-analysis on five trials comprising 871 patients, including 82% of NPC patients and 62% of patients with Stage III/IV disease. The rate of Grade 2–4 xerostomia was lower in the IMRT group [HR = 0.76, 95% confidence interval (CI) 0.66–0.87; $P < 0.00001$); however, no significant differences were observed in OS or LC between both groups. Over 80% of cohorts received concomitant chemotherapy during IMRT. CCRT is believed to increase the rates of both acute and late toxicities; thus, these findings could be extrapolated on to cases of chemo-IMRT.

IMRT is considered to improve QOL, and a previous systemic review chiefly assessed patient statuses (17,18,19,20) using questionnaires for EORTC C-30, EORTC QLQ H&N35 and SF-35 (Table 4). Tribius et al. (20) performed a systemic review using literature describing QOL assessments between 2005 and 2010. This review assessed 14 studies including five prospective trials with only one RCT. IMRT significantly improved QOL scores comprising xerostomia, dry mouth, sticky saliva, eating-related domains and global QOL over those achieved with 2D or 3D CRT. Klein et al. (19) also performed a systematic review on health-related QOL (HRQOL) scores between IMRT and 2D or 3D CRT. Eighteen studies having high-quality reports of the basis of quality assessment instrument were reviewed in this report. The HRQOL scores declined after RT and returned to baseline levels within 12 months in all groups. The HRQOL score achieved by IMRT was significantly higher than that of 2D or 3D CRT. The HRQOL score achieved by CCRT was slightly worse. These two reviews were considered to have the distinct weakness of strong biases due to the basis of a retrospective analysis. In addition, QOL was difficult to measure in patients with HNSCC, and global QOL is reflected by various factors relating to patient backgrounds and QOL instruments. The benefit of IMRT for dysphagia was also systematically reviewed from 16 studies (17); however, apparent evidence could not be derived in this review. This was attributed to the reported series being limited by both insufficient assessment methods and outcome descriptions of swallowing function. It was also caused by the lack of reliable measuring instruments for swallowing function including basement assessments, and the reported series also chiefly depended on retrospective analysis. A sophisticated RCT with a multi-institutional design is needed to accurately evaluate the advantages of IMRT regard for global QOL and late toxicities apart from xerostomia.

Table 4. Comparison of QOL score in IMRT group compared with that of conventional radiotherapy group in reported series

Author	Study design	Patient number	Site	EORTC QLQ-C30					EORTC QLQ-C30 HN&35					
				Global QOL	Physical function	Role function	Cognitive function	Social function	Pain	Swallowing	Speech	Social eating	Dry mouth	Sticky saliva
Pow (12)	Prospective	51	NPC			Y							Y	Y
Fang (80)	Prospective	203	NPC	Y									Y	
Vergeer (81)	Prospective	241	H&N	Y		Y	Y	Y	Y	Y	Y	Y	Y	Y
Fang (82)	Retrospective	356	NPC	Y	Y			Y	Y	Y	Y	Y	Y	Y
Graff (83)	Retrospective	134	H&N						Y	Y		Y	Y	
Huang (84)	Retrospective	307	H&N										Y	

NPC, nasopharyngeal cancer; QOL, quality of life; Y, significantly better for IMRT group.

Optimal method for IMRT

IMRT for LA-HNSCC is routinely performed in a simultaneously integrated boost (SIB) method, in which variable doses are delivered to several CTVs for adjusted risk levels (66). Single-step optimization is typically performed during the radiation schedule, and reducing the time and labor required for treatment preparation appears to be feasible in clinical practice. A radiation dose with a lower risk level, 54–60 Gy over 6.5–7 weeks is often delivered in the SIB technique. Regarding 2D–3D CRT, 40–50 Gy is commonly delivered for prophylactic CTV; however, a slightly larger dose may be needed in the case

of SIB due to the small fraction size (<1.8 Gy per fraction), which is expected to decrease the probability of disease control. An increased dose to the surrounding organ, such as the larynx and constrictor muscle, may lead to the development of dysphagia (8,67,68). Another weakness of the SIB technique is dose variations due to anatomical changes during the IMRT session. Several studies reported that anatomical changes may cause significant shortages in the dose on PTV and/or an excessive dose to the surrounding organ (69,70). A two-step method would resolve these problems by using the standard fraction size to all target volumes with a second boost IMRT plan (69,71,72). Although the burden on staff would increase due to additional optimization processes, dose variations resulting from anatomical changes due to tumor shrinkage and body weight loss could be adjusted for. The JCOG 1015 (UMIN000005448) is a Phase II trial that is being conducted to demonstrate the feasibility of two-step IMRT with CCRT for Stage II–IVB NPC patients. A total of 75 patients are planned to have registered by October 2014, and a follow-up will be conducted until 2017. The JCOG 1208 (UMIN000014274) is a Phase II trial conducted on patients with OPC of T1–2N0–1 category, and a two-step method is also used in this trial. These multi-institutional prospective trials are expected to demonstrate the original efficacy of the two-step IMRT method for HNSCC patients.

Japanese clinical trials for HNSCC

The JCOG Radiation Therapy Study Group developed a multi-institutional Phase II trial (JCOG 0403) on stereotactic body radiotherapy for Stage I non-small cell lung cancer in 2003. The group then expanded the trial to include several prospective trials including those for HNSCC. To date, the group has conducted a multi-institutional RCT trial to demonstrate the efficacy of AF for glottic cancer of the T1–2N0 category (JCOG 0701), a Phase II trial on chemo-IMRT for LA-NPC (JCOG 1015), and a Phase II trial on IMRT for early OPC (JCOG 1208). The Head and Neck Cancer Study Group of JCOG has conducted a Phase II/III study on post-operative chemoradiotherapy for LA-HNSCC, comparing the administration of cisplatin in a three weekly arm to a weekly arm (JCOG 1008) (73). This trial has made amendments for the use of IMRT in credentialed institutes in collaboration with the Radiation Therapy Study Group.

Apart from the JCOG group trial, a Phase II trial is being conducted on chemo-IMRT for cervical esophageal cancer (JROSG 12-1 UMIN000009880) and is supported by a National Grant Aid. The findings of these prospective trials will greatly impact on Japanese clinical practices and future trials.

Future perspective

Proton beam therapy (PBT) is expected to have the advantage of sparing normal tissue over photon beam. As for carbon-ion therapy, the high value of its relative biological effect may be beneficial for tumor control. A systemic review has discussed the benefits of particle therapy (74,75). Regarding carbon-ion therapy, survival advantages for mucosal malignant melanomas would be reported to some extent (75). The advantages of PBT for survival and tumor control in paranasal and sinonasal cancers have been reported previously (76). However, limited clinical data are available to demonstrate that toxicity is slightly lower for PBT than for photon therapy. Since the overall quantity and quality of data regarding particle therapy is poor, prospective multi-institutional data are needed in the future (75). Intensity modulated proton therapy (IMPT) is one of the promising methods that can improve the quality of definitive RT for HNSCC (75,77). IMPT has the distinct advantage of sparing normal tissue, especially with low dose exposure (77). IMPT is expected to have further advantages; thus, prospective trials on IMPT are warranted to demonstrate its benefits over IMRT.

Biomarkers play important roles in the selection of treatment modalities and/or estimation of treatment outcomes; however, reliable information has not yet been reported for HNSCC. Biomarkers to predict the outcome of CCRT and BRT are needed (78,79), and would be very helpful for both decision-making for optimal treatments and reduction of intensive multidisciplinary therapy.

Conclusion

AF, CCRT and BRT have advantages over standard fractionated radiotherapy; however, the management of both acute and late toxicities has become more important in clinical practice. Although CCRT using high dose cisplatin is the mainstay for LA-HNSCC, late toxicities were reported to increase in association with survival disadvantages. IMRT is believed to be useful for minimizing morbidity and mortality related to definitive RT, especially in the case of CCRT. Further improvements are warranted through the optimal use of adaptive radiotherapy and particle therapy.

Multi-agent induction chemotherapy with BRT represents on attractive option for balancing efficacy and toxicity, and is now being eagerly tested in prospective trials. In the future, customized therapy designed with biomarkers is desired to optimize definitive radiotherapy.

Acknowledgements

We wish to express our special appreciation to all the staff at the participating institutes of JCOG 0701, JCOG 1008, JCOG 1015 and JCOG 1208 trial, and JCOG Data Center.

Funding

The work was partially supported by Health Sciences Research Grants for a Grant-in-Aid for Cancer Research (20S-5, 20S-6, 17-17, 16-12, 17S-5 H21-018, H23-009, H24-007, H26-090) from the Ministry of Health, Labor and Welfare of Japan and the National Cancer Center Research and Development Funds (23-A-16, 23-A-21 and 26-A-4).

Conflict of interest statement

None declared.

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JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2015, 45(1) 2–6
doi: 10.1093/jjco/hyu195
Advance Access Publication Date: 19 November 2014
Review Article

Review Article

Adjuvant treatment for post-operative head and neck squamous cell carcinoma

Naomi Kiyota[1,*], Makoto Tahara[2], and Masato Fujii[3]

[1]Department of Medical Oncology/Hematology, Kobe University Hospital, Kobe, [2]Department of Head and Neck Medical Oncology, National Cancer Center Hospital East, Chiba, and [3]Department of Otolaryngology, National Hospital Organization Tokyo Medical Center, Tokyo, Japan

*For reprints and all correspondence: Naomi Kiyota, Department of Medical Oncology and Hematology, Kobe University Hospital, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan. E-mail: nkiyota@med.kobe-u.ac.jp

Received 14 September 2014; Accepted 27 October 2014

Abstract

One of the mainstays of treatment for locally advanced head and neck squamous cell carcinoma is surgery. However, for post-operative patients with high-risk factors for recurrence, surgery alone is insufficient and improving survival requires adjuvant treatment after surgery. Unlike with most other malignancies, the standard adjuvant treatment for post-operative head and neck cancer patients with high-risk factors for recurrence is radiotherapy concurrent with chemotherapy. This review article focuses on the history and future perspectives of adjuvant treatment for post-operative head and neck squamous cell carcinoma.

Key words: head and neck cancer, high-risk factors for recurrence, adjuvant treatment, chemoradiotherapy

Introduction

According to cancer statistics in Japan, 8120 Japanese died from head and neck cancer in 2012, accounting for 2.2% of cancer deaths (1). About half of head and neck cancer patients have Stage III/IV at diagnosis disease and the prognosis of these patients remains poor. Previously, surgery was one of the mainstays of treatment for resectable locally advanced head and neck squamous cell carcinoma (HNSCC), while post-operative radiotherapy (RT) was standard treatment in patients with high-risk factors for recurrence in pathological specimens (2). However, local relapse and distant metastasis relapse rates after post-operative RT were as high as 30 and 25%, respectively, and 5-year survival rate was as low as 40% (3). To improve the prognosis of post-operative HNSCC with high-risk features, the addition of cisplatin to RT was developed, and showed a survival benefit over RT alone. Now chemoradiotherapy (CRT) with cisplatin (CDDP) at a dose of 100 mg/m^2 is the standard of care for post-operative HNSCC with high-risk factors for recurrence. This review article focuses on the history and future perspectives of adjuvant treatment for post-operative HNSCC.

Adjuvant treatment for post-operative HNSCC

Which patients should receive adjuvant treatment?

The prognosis for Stage III/IV resectable locally advanced HNSCC is poor. Known risk factors for recurrence are: microscopic resection margin-positive, extracapsular nodal extension-positive, multiple cervical lymph node metastasis (≥2), lymph node metastasis with a diameter of 3 cm or more, perineural invasion, Level 4 (inferior internal jugular lymph node) or Level 5 (accessory nerve lymph node) lymph node metastasis in oropharyngeal cancer/oral cavity cancer and signs of vascular tumor embolism. For patients with none of these risk factors, 5-year local relapse rate is only 10%, and post-operative adjuvant treatment is therefore not usually performed. For patients with risk factors for recurrence, post-operative RT has been used as a post-operative adjuvant treatment. However, patients positive for extracapsular nodal extension or those with two or more risk factors for recurrence were reported to have a 5-year local relapse rate of 32% and 5-year survival rate of 42%, showing poor prognosis even after post-operative radiotherapy (4,5). Surgery with post-operative RT is therefore considered insufficient, and more effective treatment has been sought (6).

It is therefore necessary to identify the most important risk factors for recurrence in patients receiving post-operative radiotherapy. A combined analysis was conducted using data from the RTOG 85-03 study (randomized study to compare post-operative radiation with chemotherapy with 5FU + CDDP followed by post-operative radiotherapy in post-operative patients with locally advanced hypopharynx squamous cell carcinoma) and RTOG 88-24 study (Phase II study of post-operative chemoradiotherapy with CDDP in patients after surgery of locally advanced head and neck squamous cell carcinoma) conducted by the Radiation Therapy Oncology Group (RTOG) (6). Results showed that patients with risk factors for recurrence including (i) microscopically positive resection margin, (ii) extracapsular nodal extension-positive and (iii) multiple lymph node metastases (≥2) had a higher 5-year local relapse rate (microscopically positive resection margin vs. extracapsular nodal extension/multiple cervical lymph node metastasis vs. no relapse risk factor: 61 vs. 27 vs. 17%) and decreased 5-year survival rate (microscopically positive resection margin vs. extracapsular nodal extension/multiple cervical lymph node metastasis vs. no relapse risk factor: 27 vs. 34 vs. 53%) compared with patients with none of the above factors. On this basis, improving prognosis in patients with any of these three risk factors for recurrence is particularly important.

In addition to (i) microscopic resection margin positivity and (ii) extracapsular nodal extension positivity, the European Organization for Research and Treatment of Cancer (EORTC) also suggests that Stage III/IV disease, perineural infiltration, Level 4/5 lymph node metastasis in oropharyngeal cancer/oral cavity cancer, and signs of vascular tumor embolism are also risk factors for recurrence (7–10). Despite some differences in the definition of post-operative risk factors for recurrence between the EORTC and RTOG, the two key trials (Table 1), namely the EORTC22931 study (7) and RTOG95-01 study (11), were conducted, as described later. To account for these differing definitions, data from the two studies were consolidated in a combined analysis (8). This indicated not only that CRT with CDDP was generally superior to RT alone as post-operative adjuvant treatment, with the difference between them being significant [hazard ratio (HR), 0.776], but also that post-operative CRT with CDDP is more advantageous than RT alone for patients with either of the common high-risk factors for recurrence observed in the two studies, namely (i) microscopic resection margin positivity or (ii) extracapsular nodal extension positivity (HR = 0.702). In contrast, post-operative CRT with CDDP showed no advantage over RT alone in patients with risk factors for recurrence that were not common between the two studies (e.g. multiple lymph node metastases) in either the EORTC22931 study or the RTOG95-01 study.

Therefore, major high-risk factors for recurrence are presently defined as (i) microscopic resection margin positivity and (ii) extracapsular nodal extension positivity, and patients with either of these major risk factors should receive post-operative CRT with CDDP. Other risk factors for recurrence which were not common between the two studies, including multiple cervical lymph node metastases, are termed intermediate risk factors. The provision of post-operative RT to patients with these intermediate risk factors is based on the results of this combined analysis.

Table 1. Differences in risk factors for recurrence between RTOG and EORTC

Risk factor only in RTOG	Common risk factors with RTOG and EORTC	Risk factors only in EORTC
Multiple lymph node metastases (≥2)	Microscopic resection margin positivity, extracapsular nodal extension positivity	Stage III/IV disease, perineural infiltration, level 4/5 lymph node metastasis in oropharyngeal cancer/ oral cavity cancer, vascular tumor embolism

What is the optimal adjuvant treatment for post-operative high-risk HNSCC patients?

Radiotherapy

Prognosis of Stage III/IV resectable locally advanced head and neck squamous cell carcinoma is poor, and post-operative RT after radical resection has remained the standard treatment for this type of cancer since 1970, when Fletcher et al. (2) published a report on prognosis after post-operative radiotherapy. In conventional post-operative radiotherapy for resectable locally advanced head and neck squamous cell carcinoma, a total dose of 60–66 Gy is commonly used and administered once daily, five times per week at 2.0 Gy as conventional fractionated irradiation with no interval period (7,11). However, local relapse and distant metastasis relapse rates after post-operative radiotherapy were as high as 30 and 25%, respectively, and 5-year survival rate was as low as 40% (3). Thus, post-operative RT is now indicated for patients with intermediate risk factor for recurrence and those at high risk for recurrence who are unsuitable for post-operative CRT due to poor organ function (renal impairment etc.).

Chemoradiotherapy

As described above, post-operative CRT has been developed for the treatment of locally advanced HNSCC in patients at high risk of recurrence. Pivotal randomized trials of post-operative CRT for HNSCC patients at high risk of recurrence are listed in Table 2.

Bachaud et al. reported the results of a randomized comparative study in 83 HNSCC patients with high post-operative risk (extracapsular nodal extension-positive). The RT-alone group had a 5-year overall survival (OS) of 13% whereas that in the CRT (CDDP 50 mg/body every week) group was 36% ($P < 0.01$), showing the statistically significant superiority of post-operative CRT (12).

Smid et al. compared RT alone with CRT using mitomycin (MMC) and bleomycin (BLM) in 114 HNSCC patients with high post-operative risk (microscopic resection margin positivity, extracapsular nodal extension positivity, perineural invasion or signs of vascular infiltration). Although this was a small randomized study, 2-year OS was 64% in the RT-alone group versus 74% in the CRT group, showing that post-operative CRT was significantly superior ($P = 0.036$) (13).

The EORTC22931 study registered 334 patients with any of the risk factors for recurrence of microscopic resection margin positivity, extracapsular nodal extension positivity, Stage III/IV disease, perineural invasion, Level 4 or Level 5 lymph node metastasis (in oropharyngeal/oral cavity cancer), and signs of vascular tumor embolism. Five-year disease-free survival (DFS) was 36% in the RT alone vs. 47% ($P = 0.04$) in the CRT with CDDP groups, and 5-year OS was 40% vs. 53% ($P = 0.02$), showing the superiority of post-operative CRT (7).

The RTOG95-01 study registered 416 patients with any of the post-operative risk factors for recurrence (microscopic resection margin positivity, extracapsular nodal extension positivity or multiple cervical lymph node metastases (≥2). The 2-year local control rate (LCR), the primary endpoint, in the RT alone and CRT groups was 72 vs.

Table 2. Pivotal randomized trials of post-operative chemoradiotherapy

Author		Disease status	*N*	Chemo	RT total, Fr size	LRR	DFS	OS
Bachaud (1996)	5-year data (2-year data)	High risk	39	W-CDDP	65–74 Gy,	23%	45% (68%)	36% (72%)
			44	None	1.7–2 Gy/Fr	41%	23% (44%)	13% (46%)
						$P = 0.08$	$P < 0.02$	$P < 0.01$
Smid (2003)	2-year data	High risk	59	MMC,BLM	56–70 Gy,	14%	76%	74%
			55	None	2 Gy/Fr	31%	60%	64%
						$P = 0.037$	NS	$P = 0.036$
Bernier (2004)	5-year data	High risk	167	3W-CDDP	66 Gy,	18%	47%	53%
			167	None	2 Gy/Fr	31%	36%	40%
						$P = 0.007$	$P = 0.04$	$P = 0.02$
Cooper (2004)	3-year data	High risk	206	3W-CDDP	60–66 Gy,	18%	47%	56%
			210	None	2 Gy/Fr	28%	36%	47%
						$P = 0.01$	$P = 0.04$	$P = 0.19$
Fietkau (2006)	5-year data	High risk	226	5FU,CDDP	50–64 Gy	11%	62%	58%
			214	None	2 Gy/Fr	28%	50%	49%
						$P = 0.0006$	$P = 0.023$	NS
Argiris (2008)	5-year data	High risk	36	CBDCA	59.4 Gy	22%	49%	51%
			36	None	1.8 Gy/Fr	28%	53%	44%
						NS	NS	NS

Chemo, chemotherapy; LRR, local relapse rate; DFS, disease-free survival; OS, overall survival; NS, not significant; Gy, gray; Fr, fraction.

82% ($P = 0.003$) (Gray's test), respectively, showing the superiority of post-operative CRT. In addition, the 3-year progression-free survival (PFS) rate was 36 vs. 47% ($P = 0.04$), again showing the superiority of post-operative CRT. However, 3-year OS was 47 vs. 56%, showing only a trend for the superiority of post-operative CRT, without statistical significance ($P = 0.19$) (11).

At the American Society of Clinical Oncology (ASCO) meeting of 2006, Fietkau et al. (14) presented the results of ARO 96-3, a Phase III study, which compared two post-operative adjuvant treatments: RT alone and CRT with 5-FU + CDDP. This study targeted 440 HNSCC patients with high post-operative risk [microscopic resection margin positivity, extracapsular nodal extension positivity or multiple cervical lymph node metastases (≥3)]. Five-year DFS in the RT alone and CRT groups was 50 vs. 62%, respectively ($P = 0.023$), showing the statistically significant superiority of post-operative CRT, whereas 5-year OS was 49 vs. 58%, respectively, showing no significant difference.

In 2008, Argiris et al. (15) reported the results of a Phase III study on post-operative adjuvant treatment which compared RT alone and CRT with carboplatin in 72 HNSCC patients with high-risk factors (microscopic resection margin positivity, extracapsular nodal extension positivity, perineural invasion or signs of vascular infiltration). In this study, the CRT group showed no superiority to the RT-alone group in either 5-year DFS or 5-year OS, and thus the usefulness of post-operative CRT with carboplatin was not demonstrated.

Regarding the toxicities, acute/late toxicities and statistical comparisons were not consistently reported. Cooper et al. (11) reported that severe acute toxicities in RTOG95-01 study were significantly higher in CRT than RT alone (77 vs. 34%, $P < 0.001$). Moreover, Bachaud et al. (12) also reported that severe acute toxicities tended to be higher in CRT than RT alone (41 vs. 16%) (16). But, in terms of severe late toxicities, there were no significant differences between CRT and RT alone (RTOG95-01; 21 vs. 17%, EORTC22931; 38 vs. 49%) (7,11,16).

Based on the above results and combined analysis of RTOG95-01 study and EORTC22931 study (8), post-operative CRT has been the standard post-operative adjuvant treatment for HNSCC patients at high risk of recurrence (microscopic resection margin positivity or extracapsular nodal extension positivity). CDDP 100 mg/m^2 every 3 weeks, which was used in both the EORTC22931 and RTOG95-01 studies, is believed to be the most common standard regimen for concurrent monotherapy. Regarding the feasibility of post-operative CRT with CDDP at a dose of 100 mg/m^2 in Japanese patients, a Phase II feasibility study (17) reported that 80% (20/25) of patients completed per-protocol treatment. In addition, the safety profile of the study was almost the same as that of the previous studies (7,11) of post-operative CRT with CDDP at a dose of 100 mg/m^2. Thus, post-operative CRT with CDDP at a dose of 100 mg/m^2 is feasible and is the standard of care for Japanese HNSCC patients with high post-operative risk.

Chemotherapy

The role of adjuvant chemotherapy remains to be determined. Concurrent administration of chemotherapy with RT has been investigated since the 1970s, and a few randomized studies of adjuvant chemotherapy for post-operative HNSCC (18–21) have appeared. However, all of these randomized studies comparing treatment for post-operative HNSCC with or without adjuvant chemotherapy failed to show efficacy in this setting. Reports on post-operative adjuvant chemotherapy are also limited in Japan, with only a single study by Tsukuda et al. (22) in 1994, which reported that post-operative adjuvant chemotherapy with UFT significantly decreased distant relapse rate but did not contribute to survival prolongation. Thus, adjuvant chemotherapy is not indicated for post-operative HNSCC patients.

When should post-operative RT or CRT be started?

Appropriate timing to start post-operative RT or CRT is important because theoretically, excessive time from surgical resection will allow the repopulation of microscopic residual tumors, and the efficacy of adjuvant treatment will accordingly decrease. Ang et al. randomized post-operative high-risk HNSCC patients to a total dose of 63 Gy delivered over 5 or 7 weeks. In the 7-week schedule, a prolonged interval between surgery and post-operative RT was associated with significantly lower local control and survival. Overall treatment time from surgery to completion of post-operative RT had a major influence on the 5-year locoregional control rate: for an overall time of <11

weeks, locoregional control was achieved in 76%, compared with 62% for 11–13 weeks and 38% for >13 weeks ($P = 0.002$) (5). This result indicated that post-operative RT should preferably start within 6 weeks after surgery.

Future perspectives for adjuvant treatment for post-operative HNSCC

Adjuvant CRT with CDDP is the current standard treatment for high-risk post-operative HNSCC patients. Despite this treatment strategy, 5-year overall survival in this setting is still ~50% (7,11). Moreover, only 60% of patients in pivotal Phase III trials (7,11) received three cycles of CDDP at a dose of 100 mg/m^2. These findings indicate the need for more efficacious and less toxic adjuvant CRT.

Regarding investigations for more efficacious adjuvant CRT, Harrington et al. reported the final results of a randomized Phase III trial of adjuvant CRT with or without lapatinib for post-operative high-risk HNSCC patients. Lapatinib is a tyrosine kinase inhibitor with targets both EGFR and HER2. Primary endpoint of this study was DFS. Results showed no significant difference in DFS between arms (HR 1.10, 95% CI: 0.85–1.43) and no significant difference between arms in OS, the secondary endpoint (HR 0.96, 95% CI: 0.73–1.25). Taking this result together with that of the RTOG0522 trial, which compared CRT with or without cetuximab in locally advanced HNSCC and also failed to show a survival benefit for cetuximab, the addition of a molecular targeting agent to CRT provides no superiority over CRT. Other approaches may be necessary.

One of the concerns of adjuvant CRT with CDDP at dose of 100 mg/m^2 is insufficient compliance with CDDP delivery, and the use of CRT with weekly CDDP in adjuvant settings has been poorly investigated (12,23,24). CRT with weekly CDDP at 40 mg/m^2 has already shown a survival benefit for nasopharyngeal cancer (25). CRT with weekly CDDP at this dose appears to be safer and more feasible than CRT with CDDP at 100 mg/m^2. However, a small randomized trial (26) showed significantly higher rates of radiation mucositis and overall toxicities for CRT with CDDP at 40 mg/m^2. To clarify these discrepant findings for the safety and efficacy of 3-weekly and weekly schedules, we are now conducting a Phase II/III trial of post-operative chemoradiotherapy comparing 3-weekly with weekly cisplatin in high-risk patients with squamous cell carcinoma of the head and neck, the JCOG1008 study (UMIN Clinical Trial Registry number: 000009125) (27).

Conclusions

Standard adjuvant treatment for post-operative high-risk HNSCC patients is CRT with 3-weekly CDDP at dose of 100 mg/m^2. However, both compliance and treatment outcomes with this schedule are unsatisfactory, and further investigation for more efficacious and feasible adjuvant CRT is warranted.

Conflict of interest statement

None declared.

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Effects of Aprepitant on the Pharmacokinetics of Controlled-Release Oral Oxycodone in Cancer Patients

Yutaka Fujiwara[1,3]*, Masanori Toyoda[1], Naoko Chayahara[1], Naomi Kiyota[1], Takanobu Shimada[1], Yoshinori Imamura[1], Toru Mukohara[1,2], Hironobu Minami[1,2]

1 Division of Medical Oncology/Hematology, Kobe University Graduate School of Medicine, Kobe, Japan, 2 Cancer Center, Kobe University Graduate School of Medicine, Kobe, Japan, 3 Division of Investigational Cancer Therapeutics, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center Hospital, Chiba, Japan

Abstract

Purpose: Oxycodone is a μ-opioid receptor agonist widely used in the treatment of cancer pain. The predominant metabolic pathway of oxycodone is CYP3A4-mediated N-demethylation to noroxycodone, while a minor proportion undergoes 3-O-demethylation to oxymorphone by CYP2D6. The aim of this study was to investigate the effects of the mild CYP3A4 inhibitor aprepitant on the pharmacokinetics of orally administered controlled-release (CR) oxycodone.

Method: This study design was an open-label, single-sequence with two phases in cancer patients with pain who continued to be administered orally with multiple doses of CR oxycodone every 8 or 12 hours. Plasma concentration of oxycodone and its metabolites were measured up to 8 hours after administration as follows: on day 1, CR oxycodone was administered alone; on day 2, CR oxycodone was administered with aprepitant (125 mg, at the same time of oxycodone dosing in the morning). The steady-state trough concentrations (Css) were measured from day 1 to day 3.

Results: Aprepitant increased the area under the plasma concentration-time curve (AUC_{0-8}) of oxycodone by 25% ($p<0.001$) and of oxymorphone by 34% ($p<0.001$), as well as decreased the AUC_{0-8} of noroxycodone by 14% ($p<0.001$). Moreover, aprepitant increased Css of oxycodone by 57% ($p=0.001$) and of oxymorphone by 36% ($p<0.001$) and decreased Css of noroxycodone by 24% ($p=0.02$) at day 3 compared to day 1.

Conclusions: The clinical use of aprepitant in patients receiving multiple doses of CR oxycodone for cancer pain significantly altered plasma concentration levels, but would not appear to need modification of the CR oxycodone dose.

Trial Registration: UMIN.ac.jp UMIN000003580.

Citation: Fujiwara Y, Toyoda M, Chayahara N, Kiyota N, Shimada T, et al. (2014) Effects of Aprepitant on the Pharmacokinetics of Controlled-Release Oral Oxycodone in Cancer Patients. PLoS ONE 9(8): e104215. doi:10.1371/journal.pone.0104215

Editor: Emanuel F. Petricoin, George Mason University, United States of America

Received March 21, 2014; **Accepted** July 1, 2014; **Published** August 14, 2014

Funding: This study was supported by a grant for Research on Applying Health Technology from the Ministry of Health, Labour, and Welfare of Japan and Yokoyama-Rinsyo foundation. However, the funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* Email: yutakafu@ncc.go.jp

Introduction

Oxycodone is a μ-opioid receptor agonist which is widely used in the treatment of cancer pain and chronic pain [1]. It is a semi-synthetic form of morphine with similar analgesic properties and side effects such as nausea, vomiting, constipation, somnolence, dizziness and pruritus [2]. At high dose or overdoses, oxycodone can cause shallow respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, etc. The oral bioavailability of oxycodone is 60 to 87%, and is higher than that of morphine [3–5]. Only 10% of the oxycodone dose is excreted unchanged in the urine and it is extensively metabolized by duodenal and hepatic cytochrome P450 (CYP) isozymes [6] [7]. The predominant metabolic pathway of oxycodone is CYP3A4-mediated N-demethylation to noroxycodone, while a minor proportion undergoes 3-O-demethylation CYP2D6 to oxymorphone, which is the active metabolite. Further oxidation of these metabolites via CYP2D6 (and CYP3A4) yields noroxymorphine [6]. Both of these metabolites are further metabolized into noroxymorphine.

Aprepitant, an orally available, selective neurokinin-1 receptor agonist, is effective for both acute and delayed chemotherapy-induced nausea and vomiting (CINV) and is used in combination with a 5-hydroxytryptamine-3 ($5HT_3$) antagonist and a corticosteroid (e.g., dexamethasone) for the treatment of moderately and highly emetogenic chemotherapy. The recommended dose of aprepitant is 125 mg prior to chemotherapy on day 1 and 80 mg once daily on days 2 and 3 (125-mg/80-mg regimen).

Aprepitant is metabolized by CYP isozymes 1A2, 2C19, and 3A4, and was shown to be a moderate inhibitor of CYP3A4 (K_i of about 10 μM for 1′ and 4-hydroxylation of midazolam and N-demethylation of diltiazem, respectively) in vitro and a very weak inhibitor of CYP2C19 and CYP2C9 [8]. Moreover, drug-drug interaction studies have indicated that aprepitant can inhibit CYP3A4 enzyme activity. When the standard oral dexamethasone regimen for CINV (20 mg on day 1 and 8 mg on days 2 to 5) was

given concomitantly with aprepitant, the dexamethasone area under the time-concentration curve (AUC) from 0 to 24 hours increased approximately 2-fold on both day 1 and day 5 compared with the standard oral dexamethasone regimen alone [9]. When the methylprednisolone regimen consisted of 125 mg intravenously on day 1 and 40 mg orally on days 2 to 3, aprepitant increased the AUC of intravenous methylprednisolone 1.3-fold on day 1 and of oral methylprednisolone 2.5-fold on day 3 [9]. Conversely, several studies have not demonstrated that aprepitant use mediated clinically relevant effects on the pharmacokinetics of intravenously administered docetaxel or vinorelbine [10] [11].

At the 125-mg/80-mg regimen used for oral aprepitant administration for CINV, the peak plasma concentrations (Cmax) of 1,600 ng/mL (around 3.0 μM) and 1,400 ng/mL (around 2.6 μM) were reached in approximately 4 hours (Tmax) on day 1 and day 3, respectively [12]. As the intestinal drug concentration following oral administration is even higher than the plasma concentration, it is expected that orally-administered aprepitant inhibits intestinal CYP3A4 greater than intravenously-administered aprepitant and that orally co-administered drug is affected to a greater extent by the inhibitory effect of intestinal CYP3A4 than intravenously co-administered drug [9,13].

Concomitant use of oxycodone and aprepitant is used in clinical practice for cancer patient care. However, aprepitant might have the potential to increase the plasma concentrations of oxycodone and its metabolites via inhibition of CYP3A-mediated metabolism of oxycodone. As a result, the side effects of oxycodone may increase. In this study, we have therefore investigated the possible effects of the mild CYP3A4 inhibitor aprepitant on the pharmacokinetics of orally administered CR oxycodone in patients with cancer pain.

Methods

The protocol for this trial and supporting TREND checklist are available as supporting information; see Checklist S1, Protocol S1 and S2.

Patient selection criteria

The subjects were enrolled in patients whom continued to be administered CR oxycodone twice or three times daily for cancer pain and were planned to receive chemotherapy with aprepitant for CINV. Within the last 3 or more days to reach steady state, the subjects had received a fixed dose of CR oxycodone. Additional eligibility criteria were age≧18 years, histologically confirmed malignant solid tumor, and adequate organ function [serum total bilirubin less than 1.5×upper limits of normal (ULN), aspartate aminotransferase (AST) less than 2.5×ULN, alanine aminotransferase (ALT) less than 2.5×ULN, and serum creatinine less than 1.5×ULN]. Patients were excluded if they had gastrointestinal disorders that could affect ingestion or absorption of either CR oxycodone or aprepitant, and if they were receiving or likely to receive drugs or food that could act as potent CYP3A4 or CYP2D6 inhibitors or inducers. All patients provided written informed consent and study approval was obtained from the Institutional Review Board of Kobe University Hospital.

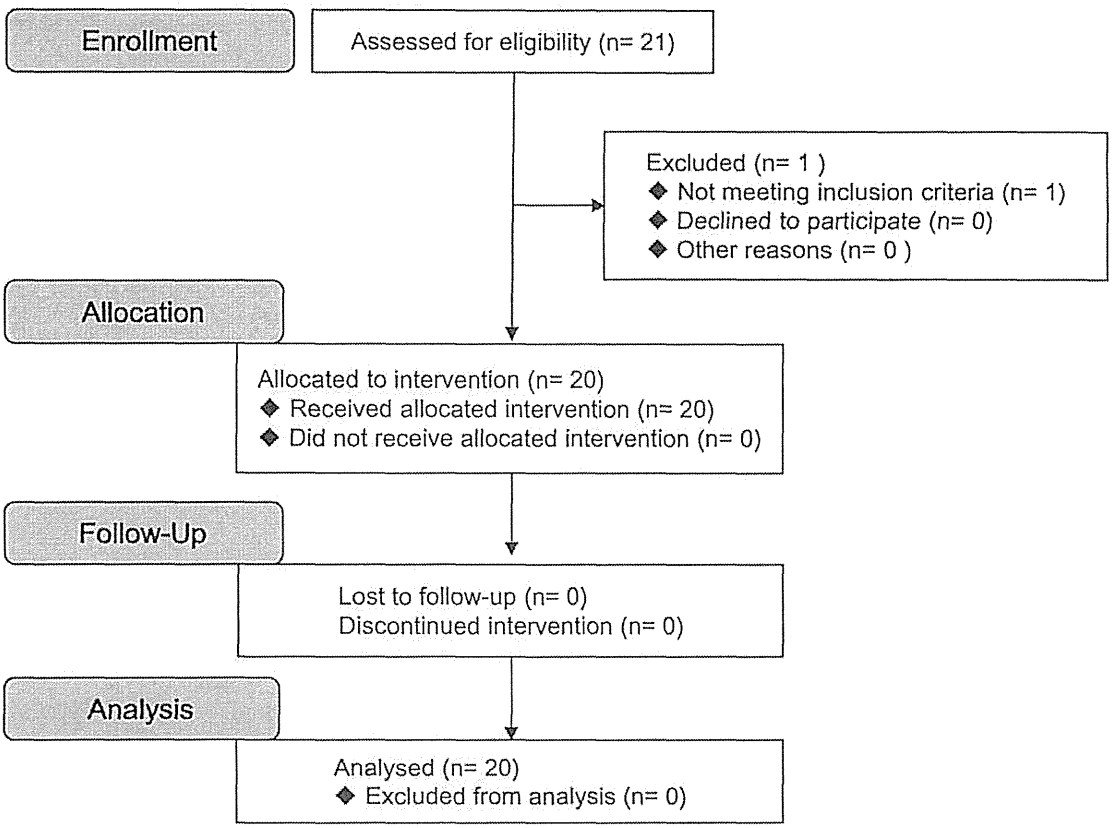

Figure 1. CONSORT flow diagram.
doi:10.1371/journal.pone.0104215.g001

Table 1. Patient characteristics.

		Number of Patients (n = 20)
Gender	Male/female	17 (85%)/3 (15%)
Age	Median (range)	66.5 (44–77)
ECOG PS	1/2	13 (65%)/7 (35%)
Height (cm)	Median (range)	164.4 (138.5–177.1)
Weight (kg)	Median (range)	59.6 (37–77)
BSA (m^2)	Median (range)	1.64 (1.19–1.90)
Cancer type	Pancreatic cancer	8 (40%)
	Head and Neck cancer	4 (20%)
	NSCLC	2 (10%)
	CRC	2 (10%)
	CUP	2 (10%)
	Endometrial cancer	1 (5%)
	Cholangiocarcinoma	1 (5%)
Clinical stage	IV	20 (100%)
Anti-cancer agent	Platinum agent	8 (40%)
	Gemcitabine	7 (35%)
	Fluoropyrimidine	5 (25%)
	Taxanes	4 (20%)
	Anthracyclines	2 (10%)
	Irinotecan	2 (10%)
	Sunitinib	1 (5%)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; CUP, cancer of unknown primary.

doi:10.1371/journal.pone.0104215.t001

Study design

This study which was an open-label, two-period, single-sequence design was conducted at Kobe University Hospital. Patients were administered regularly with multiple-doses of oral CR oxycodone every 8 or 12 hours. Each patient was administered with the appropriate dose of oral CR oxycodone for their cancer pain. They received CR oxycodone alone (period A) on the previous day of planned chemotherapy and CR oxycodone with aprepitant (period B) on the day of chemotherapy. On the morning of period B, aprepitant was taken orally at the same time as CR oxycodone more than one hour prior to chemotherapy. Patients were participated in this study during blood sampling. Patients in hospital were given the dose of anticancer agents according to standard treatment schedule for their tumor types and were allowed to receive an antiemetic treatment with dexamethasone and a $5HT_3$ receptor antagonist where appropriate.

Outcome

The study objective was to investigate aprepitant might have the potential to increase the plasma concentrations of oxycodone and its metabolites via inhibition of CYP3A-mediated metabolism of oxycodone. The primary endpoint was pharmacokinetics of oxycodone and its metabolites with and without aprepitant administration. Secondary endpoints were safety and adverse event including nausea, vomiting, constipation, and somnolence. Patient characteristics and medication information were recorded

Table 2. Dose of Oxycodone.

Dose	Frequency of administration	Daily dosage	Number of patients
5 mg	every 12 hours	10 mg	6 (30%)
	every 8 hours	15 mg	2 (10%)
10 mg	every 12 hours	20 mg	6 (30%)
	every 8 hours	30 mg	3 (15%)
15 mg	every 12 hours	30 mg	1 (5%)
20 mg	every 12 hours	40 mg	1 (5%)
	every 8 hours	60 mg	1 (5%)

doi:10.1371/journal.pone.0104215.t002