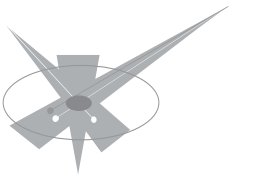
Rep Pract Oncol Radiother, 2007; 12(6): 329-337



Original Paper

Received: 2007.06.21
Accepted: 2007.09.24
Published: 2007.12.27

Cisplatin-based chemotherapy: the only alternative in chemoradiation of head and neck cancer? Experience of the Institute of Oncology, Ljubljana, Slovenia

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Source of support: Supported by the Slovenian Research Agency, Grant P3-0307.

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background Concomitant chemoradiation is a widely used therapeutic concept in intensified locoregional treatment of high risk head and neck cancer patients. In this context, cisplatin monotherapy or in combination with other chemotherapeutics is recognized as the most effective drug to be added to radiotherapy.

Aim The aim of this review is to present the rationale for combining radiotherapy with cisplatin in the treatment of head and neck cancer and to summarize the experience of the Institute of Oncology Ljubljana, Slovenia, gained through two prospective randomized trials on chemoradiation with mitomycin C and bleomycin in operable as well as inoperable head and neck cancer patients. Furthermore, recent developments in technology and biological drug modeling are discussed, which are considered to have a potential to add significantly to the locoregional effectiveness of radiotherapy.

Materials/Methods References were retrieved using the online data base of the National Library of Medicine (PubMed: *http://www.ncbi.nlm.nih.gov/PubMed*). Terms used included: head and neck carcinoma, squamous cell carcinoma, concomitant chemoradiotherapy, cisplatin, mitomycin C, bleomycin. The results of studies using cisplatin-based chemoradiation regimens in the treatment of patients with inoperable tumors and on postoperative stetting were compared with the results of the studies, conducted at the Institute of Oncology and ENT Department at the Clinical Center Ljubljana, Slovenia.

Results When comparing mitomycin C-bleomycin chemotherapy with other comparable series on exclusively inoperable oropharyngeal cancer, but with cisplatin (or carboplatin) and 5-fluorouracil chemotherapy, and to standard dose cisplatin regimen used in postoperative setting, the effectiveness of our unconventional drug combination appeared to be at least equivalent to the well established platinum-based chemotherapy standard.

Conclusions At the moment, concomitant chemoradiation with cisplatin-based chemotherapy is the most widely used way for potentiation of locoregional effect of radiotherapy in high risk head and neck cancer patients. Our clinical experiences with mitomycin C and bleomycin chemoradiation showed that there was still a window of opportunity to achieve equivalent clinical results with other drug combinations.

Key words head and neck carcinoma • squamous cell carcinoma • concomitant chemoradiotherapy • cisplatin • mitomycin C • bleomycin

Full-text PDF: http:/www.rpor.eu/pdf.php?MAN=11492

Word count: 3013
Tables: 2
Figures: 2
References: 32

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Background

Head and neck cancer is the sixth most prevalent cancer worldwide, with a global yearly incidence of more than 500,000, representing approximately 5% of all cancers [1]. Although early tumours are potentially curable with surgery and chemotherapy, the prognosis of patients with advanced disease has remained poor. Because the majority of randomized trials on induction chemotherapy failed to prove any survival benefit in this poor prognosis group of patients, research has focused on the concurrent use of chemotherapy and irradiation [2].

The concept of concurrent application of chemotherapy and irradiation has been investigated since the 1960s [2]. The main rationale for such treatment is to increase local control by overcoming radioresistance and to eradicate systemic micrometastases. Another important aim of combining chemotherapy and radiotherapy is to preserve the function and cosmesis of treated organs, which could be severely deteriorated by using extensive and mutilating surgery as the only therapy or part of the treatment package.

The most significant potential mechanisms of interaction between chemotherapy and radiotherapy are: (*i*) to increase the steepness of the dose-response curve or to shift the curve to the left; (*ii*) to inhibit the repair of radiotherapy-induced sublethal or potentially lethal damage; (*iii*) to improve tumour oxygenation; (*iv*) to provide selective cytotoxicity for hypoxic cells or radiosensitization of hypoxic cells; and (*v*) to increase apoptosis [2,3].

Initially, radiotherapy was combined with agents like methotrexate, hydroxyurea, fluorouracil or bleomycin. In addition to systemic toxicity, each of these drugs also induces inflammation of oral, pharyngeal and laryngeal mucosa. Consequently, the local side-effects of irradiation are intensified, which results in poor patient compliance and prolongation of therapy. No improvement in overall survival when compared with irradiation alone was observed in clinical trials [2].

The first breakthrough in chemoradiation of head and neck carcinoma was the introduction of cisplatin to clinical practice in the early 1970s. Nowadays, cisplatin is used in a variety of treatment schedules and, at the moment, it is considered a standard drug in concomitant chemoradiation protocols. It is the best characterized currently available radiosensitizer and possesses all the mechanisms of interaction with irradiation summarized above [3]. A cisplatin dose of 100mg/m^2 administered in 3-week intervals, concomitantly with radiotherapy, is considered as a standard. In this respect, it is important to take into account the observation from several clinical studies suggesting that a cumulative cisplatin dose of approximately 200mg/m^2, independent of treatment schedule, might be sufficient to yield a beneficial anti-tumour effect. Lower but still effective cisplatin doses, applied on a weekly or daily basis, should result in a more favourable toxicity profile and better compliance with combined therapy [4].

Why cisplatin?

There are numerous combinations of various drugs that have been tested in clinical trials such as (*i*) carboplatin – a second-generation platinum drug, mimicking the radiopotentiation properties of cisplatin with a somewhat different toxic profile [3]; (*ii*) mitomycin C – a bioreductive alkylating agent, activated enzymatically under hypoxic conditions and selectively toxic for hypoxic cells, but not for well oxygenated cells in tumour surrounding [5]; (*iii*) taxanes – antimitotic agent that promote tubulin polymerization and the formation of stable microtubules [6]; (*iv*) gemcitabine – a nucleoside analogue with

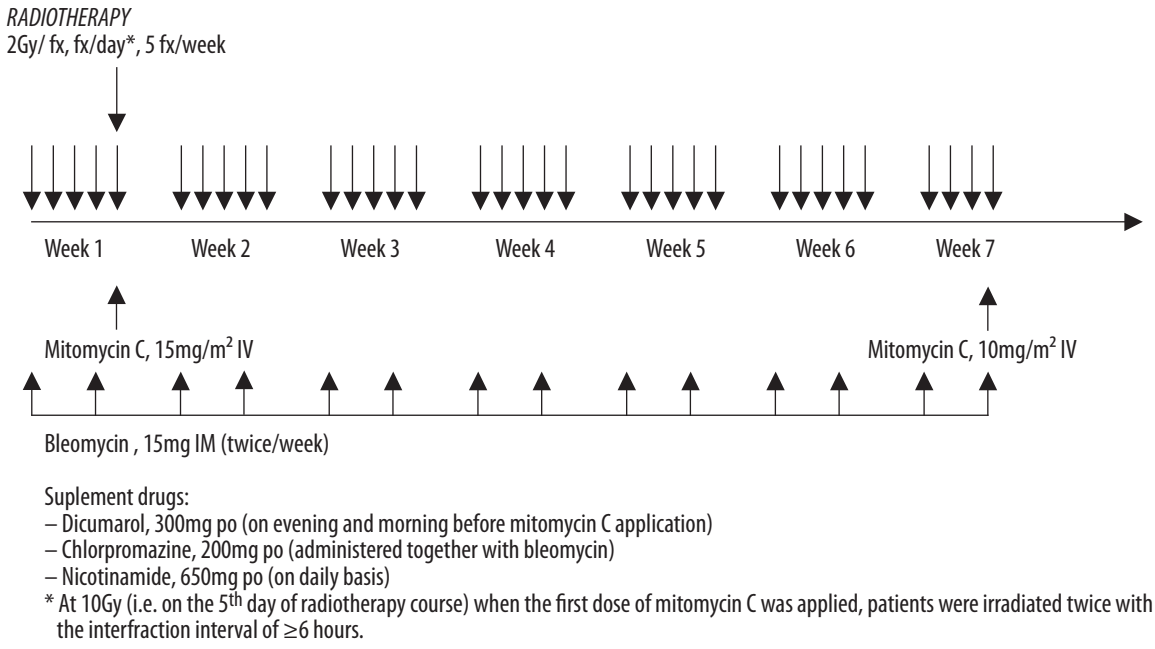

Figure 1. Concomitant chemoradiotherapy with mitomycin C and bleomycin – basic treatment schedule. In the study on postoperative chemoradiation, basic chemotherapy prescriptions and radiotherapy dose levels were changed as described in the text.

the ability to inhibit DNA replication and repair [6]; and many others. However, following abundant clinical experience gained over decades, cisplatin monotherapy or in combination with other chemotherapeutics has become the drug of choice in the majority of concomitant chemoradiation protocols [4].

The most convincing evidence of the effectiveness of concurrent chemoradiotherapy in non-metastatic squamous cell carcinoma of the head and neck and of the central role of cisplatin in the chemotherapy part of these protocols was provided by the MACH-NC meta-analysis in 2000 and its update in 2004. In this meta-analysis, individual patient data from 63 randomized trials with more than 10,000 participants with locally advanced non-metastatic squamous cell carcinoma of the head and neck, conducted between 1965 and 1993, were analyzed. The treatment results of the study arms with or without chemotherapy were compared, and chemotherapy (irrespective of type) was found to add significantly to locoregional treatment. The analysis yielded a pooled hazard ratio of death of 0.90, corresponding to an absolute survival benefit of 4% at 5 years in favour of the chemoradiotherapy arm. Analyzing the trials by the type of chemotherapy, a survival advantage was recorded only in the group of 26 concomitant trials with altogether 3727 patients with an absolute 5-year survival benefit of 8% at 5 years and 19% reduction of the risk of death. Unfortunately, heterogeneity between trials and, consequently, of the results, prevents a firm conclusion on the extent of the benefit of concomitantly applied chemotherapy. There was no significant benefit associated with the application of adjuvant or neoadjuvant chemotherapy [7].

In an update of the MACH-HN database, 24 trials were additionally included, most of them testing concomitant chemoradiation. Altogether, 87 trials with individual data on more than 16,000 patients treated between 1965 and 2000 were analyzed, reconfirming the overall benefit of adding chemotherapy to radiotherapy. Also, in the group of 50 concomitant trials, the results were identical when comparing the 1965–1993 trials and 1994–2000 trials in the definitive and postoperative setting, but without significant heterogeneity in the recent group. The benefit was most pronounced and was significantly higher for platinum-based chemotherapy, applied as monochemotherapy or in combination with other drugs, compared to other chemotherapy regimens [8].

Experience of the Institute of Oncology, Ljubljana, Slovenia

At the Institute of Oncology, Ljubljana, and the ENT Department at the Clinical Centre Ljubljana, Slovenia, we conducted two prospective randomized trials to assess the efficacy and toxicity of simultaneous application of irradiation,

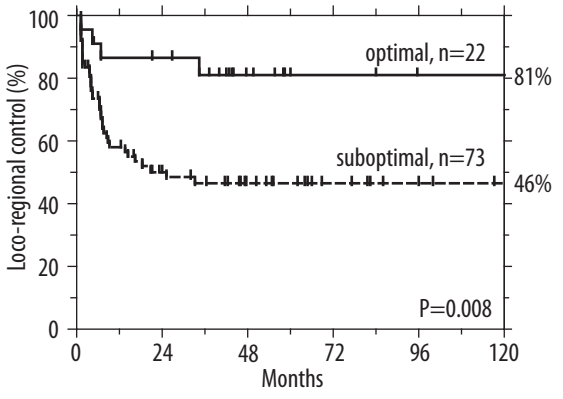

Figure 2. Survival of patients with inoperable oropharyngeal cancer (N=95) treated with concomitant chemoradiotherapy with mitomycin C and bleomycin: impact of treatment intensity.

mitomycin C and bleomycin in the treatment of patients with inoperable tumours and on postoperative setting. Radiotherapy regimen and chemotherapy schedule were the same in both studies.

Rationale for selection of chemotherapy schedule

Mitomycin C and bleomycin were selected to be administered with radiotherapy on the basis of their biochemical and pharmacological properties (Figure 1). Conventional fractionation with 2Gy daily dose delivered five times per week and 2.5-D treatment planning were used in both studies.

In advanced head and neck tumours, a high proportion of hypoxic cells can be expected, whereas mechanical perturbation of tissues during surgery gives rise to the formation of hypoxic islands inside the area of the operative bed. Consequently, the alkylating agent mitomycin C was selected due to its selective toxicity to hypoxic cells. Under hypoxic conditions, it is reductively activated by a number of oxidoreductases and, in combination with irradiation, enhances the cytodestructive effect of the latter [5]. Originally, 15mg/m^2 I.V. mitomycin C application was planned at 10Gy of radiotherapy, when the proportion of radioresistant hypoxic cells was believed to be the greatest, and the mitomycin C dose of 10mg/m^2 was to be given on the last day of radiotherapy [9,10]. Because more than only an additive effect of the drug was expected, the patients received a double dose of irradiation on the day of its first application [11]. Later on, in a postoperative setting, the second dose of mitomycin C was omitted [12,13]. To increase the effectiveness of mitomycin C on hypoxic cells, 300mg of dicumarol was applied orally in the evening and morning before mitomycin C administration [14].

To the contrary, bleomycin prevailingly acts on oxygenated cells. To minimize its toxicity and to achieve protracted resorption, a low dose intensity (5 mg twice a week) and I.M. way of application were selected [15]. To further reduce the risk of bleomycin-related pulmonary toxicity and to enhance its effect on tumour cells, 200mg of chlorpromazine was administered orally together with bleomycin [16], whereas 650mg of oral nicotinamide was given on a daily basis throughout the duration of therapy to avoid the emergence of tumour cell lines resistant to bleomycin [17]. These prescriptions were changed in the study on postoperative chemoradiation to 75mg of chlorpromazine and to 225mg of nicotinamide.

Clinical results

Inoperable tumours

Between 1991 and 1993, 64 patients with inoperable tumours, 94% of them with UICC TNM stage IV tumours, were randomly assigned to the radiotherapy arm (RT, 32 patients) and combined radiochemotherapy arm (CRT, 32 patients). The survival results were the same in the preliminary [10] as well as final report [11]. A statistically highly significant difference in favour of the combined treatment arm was observed in the tumour remission rate 2 months after the end of therapy (59% vs. 31%, P= 0.04) and the 4-year disease-free survival (37% vs. 8%, P=0.01), whereas in the overall survival, only a trend was observed (26% vs. 7%, P=0.08). However, when only the patients with oropharyngeal cancer were considered (64% of all patients), the difference between the two arms was even more pronounced and reached the level of statistical significance in all three study endpoints [11].

The significance of these results prompted us to stop the study prematurely and, after December 1993, mitomycin C-bleomycin chemoradiotherapy became the standard treatment at our institute for all eligible patients with inoperable oropharyngeal carcinoma. In the long term (median follow-up time of 85 months), in the cohort of the first 95 consecutive patients with inoperable oropharyngeal tumours, 78% of them had stage IV disease, the probability of locoregional control at 5 years was 55%, the disease-free survival 51%,

Table 1. Inoperable oropharyngeal cancer: results in experimental arm of selected prospective randomized trials on concomitant chemoradiotherapy (see text for details).

Author[Ref.]	N	Treatment	FUP	Outcome (%)			Remarks
			(yrs.)	LRC	DFS	OS	
Calais et al., 1999[19] & 2001[20]	109	RT 70Gy + 3 cycles of:	5	53	30	nr	Stages
		CARBO 70mg/m^2, days 1–4					III & IV
		5-FU 600 mg/m^2, days 1–4					
Staar et al., 2001[21]	87	IHFA RT 69.9Gy +	2	53	nr	nr	Inoperable
		CARBO 70mg/m^2, days 1–5 & 29–33					stages
		5-FU 600mg/m^2, days 1–5 & 29–33					III & IV
Olmi et al., 2003[22]	64	RT 66–70Gy + 3 cycles of:	2	nr	42	51	Stages
		CARBO 75mg/m^2, days 1–4					T1N1 & T2N1
		5-FU 1000mg/m^2, days 1–4					excluded
IOL, 2006[18]	95	RT 70Gy +	2	60	55	52	Inoperable
		MITO-C 15mg/m^2, day 5	5	56	51	34	stages
		MITO-C 10mg/m^2, day 46					III & IV
		BLEO 5mg biw					

N – number of patients, FUP – follow up, LRC – locoregional control, DFS – disease-free survival, OS – overallsurvival, RT – conventional radiotherapy, IHFA – intensified hyperfractionated accelerated, CARBO – carboplatin, 5-FU – 5-fluorouracil, MITO-C – mitomycin C, BLEO – bleomycin, biw – twice-a-week, nr – not reported, IOL – Institute of Oncology Ljubljana.

and the overall survival 32% [18]. In a multivariate model, the survival endpoints were significantly influenced by the treatment intensity (in addition to performance status and stage of disease), which clearly determined a subpopulation of patients (mitomycin C ⩾14.1mg/m^2 + bleomycin ⩾35mg + biological equivalent dose ⩾65Gy$_{10}$) with more favourable prognosis (Figure 2). When contrasting our experience with three other comparable series on exclusively oropharyngeal cancer, but with cisplatin (or carboplatin) and 5-fluorouracil chemotherapy [19–22], the effectiveness of our unconventional drug combination appeared to be at least equivalent to the well established platinum-based chemotherapy standard (Table 1). This observation imposes the presumption that the mode of therapy (induction vs. concomitant) is more important than the choice of the drugs.

Operable tumours

Between March 1997 and December 2001, 114 patients were randomly assigned after curative surgery to the postoperative radiotherapy group (RT, 55 patients) or concomitant chemoradiotherapy group (CRT, 59 patients). The patients were stratified according to the UICC pTNM stage, site of the primary tumour and presence/absence of high risk prognostic factors (i.e. extracapsular tumour spread, perineural, lymphatic or venous invasion, and residual disease) [12].

After a median follow-up time of 76 months, a significant survival advantage was confirmed in the CRT arm compared to the RT arm in respect of 5-year locoregional control (88% vs. 65%, P=0.026) and disease-free survival (53% vs. 33%, P=0.035), whereas in the case of overall survival, only a trend was observed (55% vs. 37%, P=0.091). After stratifying the patients according to the presence or absence of high risk prognostic factors (extracapsular extension and/or residual disease), the difference between RT and CRT reached the level of statistical significance only in the patients with high risk factors, but not in the low risk group. There was no difference in the rate of occurrence of distant metastases between the two treatment groups, whereas the 5-year probability of developing a second primary malignancy was higher in the RT arm (34 vs. 8%, P=0.023). Even though the chemotherapy was not designed to act on systemic metastases (as the drug doses were sufficient to enhance the effect of irradiation), it seems possible that it acts on *in situ* second primary tumours either to cure them or delay their development.

Table 2. Locally advanced head and neck cancer: results of prospective randomized trials on postoperative concomitant chemoradiotherapy.

Author[Ref.]	N	Treatment	FUP	Outcome (RT/CRT arm,%)			Remarks
			(yrs.)	LRC	DFS	OS	
Bernier et al., 2004[23]	334	RT 54–66Gy vs.	5	69/82	36/47	40/53	Locally
		RT 54–66Gy +		P=0.007	P=0.04	P=0.02	advanced
		CP 100mg/m^2, days 1, 22, 43					
Cooper et al., 2004[24]	459	RT 60–66Gy vs.	3	67/78	36/47	47/56	N2+ and/or
		RT 60–66Gy +		P=0.01	P=0.04	P=0.19	ECE and/or
		CP 100mg/m^2, days 1, 22, 43					R1
IOL, 2007[13]	114	RT 56–70Gy vs.	5	65/88	33/53	37/55	Stages
		RT 56–66Gy +		P=0.026	P=0.035	P=0.09	III & IV
		MITO-C 15mg/m^2 day 5					
		BLEO 5mg biw					

N – number of patients, FUP – follow up, RT – conventional radiotherapy, CRT – chemoradiotherapy, LRC – locoregional control, DFS – disease-free survival, OS – overall survival, CP – cisplatin, MITO-C – mitomycin C, BLEO – bleomycin, biw – twice-a-week, N2+ – two or more regional lymph involved with tumour, ECE - extracapsular extension, R1 – microscopically involved surgical margin, IOL – Institute of Oncology Ljubljana.

However, the dominating causes of death in the CRT arm were infections and distant failures, which diminished the survival gain of treatment intensification by adding chemotherapy to irradiation in high risk patients and resulted in a non-significant log-rank P-value for overall survival between the two study arms [13].

Finally, comparing our results to those of the two large trials published by Bernier et al. [23] and Cooper et al. [24], it appears that the effectiveness of our chemotherapy combination is comparable to the standard dose cisplatin regimen in all analyzed survival endpoints (Table 2).

Toxicity

As expected, acute toxic side effects to the mucosa and skin in the irradiated area, bone marrow toxicity (leukopenia, thrombocytopenia, infections) and weight loss were more severe and more frequent, although not always statistically significant, in the CRT arm compared to the RT arm in both of our trials [10,12]. As the median dose of mitomycin C administered to our patients was close to that prescribed in the protocol, indicating relatively safe systemic toxicity profile of the drug, the dose of bleomycin had to be reduced in almost all radically and all postoperatively treated patients due to severe mucositis. Even though some selectivity could probably be achieved with mitomycin C due to its selective activation in a hypoxic environment, in general the incidence of grade 3 or higher acute toxicity did not differ significantly between our study and cisplatin-based studies [19–24]. More importantly, the difference in acute toxicity profiles between various drugs seems to be more crucial for consideration when choosing the most appropriate regimen for each individual patient.

With regard to the late adverse effects of grade III or higher grade, no significant difference in the probability of their development was observed between the RT and CRT arms of our two trials [10,13]. The same was reported in several cisplatin-based studies [19–24].

Biological activity of mitomycin C-bleomycin chemotherapy

Analyzing the effectiveness of the mitomycin C-bleomycin combination, we found the dose-response curve calculated from our clinical data on inoperable oropharyngeal carcinoma to be steeper than usual. The gamma value 50 (γ_{50}, the percentage increase of local control per 1% increase of the total tumour dose at the steepest part of the curve) in our case was 2.76, whereas the γ-values (γ_{37} or γ_{50}) of oropharyngeal carcinomas reported in the literature ranging from 0.5 to 1.6. There are several characteristics of tumours and the treatment process which make –

due to their heterogeneity – the dose-response curve shallow. However, as mitomycin C selectively kills the most radioresistant, i.e. hypoxic, fraction in the tumour, the residual tumour clonogenes become more homogeneous in terms of radioresponsiveness. Consequently, the steepness of the dose-response curve is increased. Any discussion on the contribution of bleomycin to the shape of the dose-response curve, based on our clinical data, would be only speculative [18].

The next interesting observation was related to the ratio in locoregional control rate between low and high haemoglobin groups. In our study on inoperable oropharyngeal carcinoma, this ratio was 0.84 [18], whereas in another two mitomycin C trials published by Budach et al. [25] and Glaser et al. [26], the ratio was 0.82 and 0.93, respectively. When comparing these results with other published data for head and neck carcinoma where other chemotherapy regimens were used (mainly cisplatin-based) and where the ratio was generally much lower, it seemed that mitomycin C had the potential to mask the negative effect of low haemoglobin level. By acting on and reducing the hypoxic part in the tumour, mitomycin C rendered the tumour response less dependent on haemoglobin concentration [18].

Other options

With more comprehensive understanding of radiobiological principles of radiotherapy and recent developments in biological drug modelling and technology, more room for improvement in some other areas is available.

A promising upgrading of the existing concept of concomitant chemoradiation seems to be the integration of induction chemotherapy and biological agents into treatment protocols. The rationale for a sequential approach would be that the concomitant chemoradiotherapy would influence the locoregional control and the induction chemotherapy would decrease the risk of distant metastases. With the proven potential for screening tumour radiosensitivity, downstaging and decreasing the likelihood of distant metastatic disease [for a review see Ref. 27], induction chemotherapy has already shown a survival benefit when docetaxel is incorporated in the regimen [28]. Taxanes in combination with platinum compounds are currently being tested as induction chemotherapy in combination with concurrent chemoradiation in several phase III clinical trials [27].

As the great majority of squamous cell carcinomas overexpress epidermal growth factor receptor (EGFR), which has been found to be linked to poor outcome of treated patients [29,30], the inhibition of EGFR signalling is suggested as a new promising strategy in the treatment of head and neck carcinomas. The majority of efforts are focused on EGFR inhibition using small-molecule tyrosine kinase inhibitors and anti-EGFR monoclonal antibodies (e.g. cetuximab, Erbitux®). The most convincing evidence of anti-tumour effectiveness of cetuximab in squamous cell carcinoma of the head and neck when added to standard therapy was provided by the multicentre randomized phase III trial reported by Bonner et al., who compared radiotherapy with the combination of irradiation and concurrent cetuximab in patients with locoregionally advanced stage III or IV tumours [31]. The significant improvement in locoregional control in favour of combined treatment also resulted in a significant overall survival benefit in the experimental arm of the trial. Furthermore, as no overlapping toxicity was recorded between the irradiation and cetuximab, this experience initiated extensive research aiming to define the toxicity and efficacy of a triple combination consisting of cisplatin-based concomitant chemoradiotherapy and cetuximab [31]. The ongoing research results suggest that the standard dose cisplatin monotherapy (100 mg/m^2 weeks 1 and 4) in combination with irradiation (concomitant boost radiotherapy) and cetuximab is not an optimal combination, but warrants further investigation of its safety profile [32].

Conclusions

At the moment, concomitant chemoradiation with cisplatin-based chemotherapy is the most widely used way for potentiation of the locoregional effect of radiotherapy in high risk head and neck cancer patients. Recently, in the MACH-HN meta-analysis, the effectiveness of this regimen was recognized as superior to other chemotherapy schedules. However, our clinical experience gained through prospective randomized studies on chemoradiation with mitomycin C and bleomycin showed that there was still a window of opportunity to achieve equivalent clinical results with other drug combinations. Furthermore, new developments in technology, biological drug modelling and better understanding of radiobiological principles of radiotherapy create a promising basis for additional improvement in head and neck cancer management.

Acknowledgement

The article resumes the lecture given by the author during his visit to the Great Poland Centre of Oncology in Poznań on April 3, 2007.

The author thanks Professor Marjan Budihna for providing Figure 2.

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