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Cisplatin and Radiotherapy in the Treatment of Locally Advanced Head and Neck Cancer

A Review of their Cooperation

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A review of the published literature has been undertaken to ascertain the trends in treatment schedules of unresectable head and neck cancer (HNC) using cisplatin in conjunction with radiotherapy. In addition, four trials were reviewed where cisplatin was examined as a single agent without radiotherapy, demonstrating that cisplatin alone has a palliative effect only, and for a curative intent should be used in combination with radiation. Of the numerous clinical trials published on such combined chemo-radiotherapy, 16 were selected for analysis fulfilling the following criteria: cisplatin used as the sole chemotherapeutic agent in combination with radiation for patients with unresectable squamous cell carcinomas of the head and neck, with no previous treatment for the same malignancy. Daily low-dose cisplatin performed in 6 out of the 16 trials demonstrated increased tumour control with less toxicity as compared to weekly high-dose drug delivery. The increased tumour control with a daily low-dose schedule reflects the observation that cisplatin dissociates from the DNA in 24 h. Other cisplatin properties (e.g. radiosensitizing) also have the potential to influence chemo-radiotherapy treatment outcomes. There is significant scope to further optimize the treatment schedule for the unresectable HNC through detailed study of the pharmacokinetics and radiobiology of combined chemo-radiotherapy.

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Radiotherapy, chemotherapy and chemo-radiotherapy have been extensively used for the treatment of locally advanced, unresectable head and neck cancer. However, objective analysis of an optimal treatment regimen is complicated by the multiplicity of drugs and their interactions with the ionizing radiations. In an attempt to provide greater insight, the following treatise focuses on the merits of trials utilizing one chemotherapeutic agent: cisplatin (1).

As a single therapeutic agent, the clinical results with cisplatin are poor in advanced head and neck cancer, despite demonstrated effectiveness in vitro. Radiotherapy alone has an impact on the short-term prognosis of advanced head and neck cancer but the long-term benefits have been moderate (2, 3).

The majority of the trials using combined chemo-radiotherapy for locally advanced head and neck cancer have presented some promising results. Current trials tend to fractionate the drug dose with daily administration, leading to improved long-term benefits and better-tolerated treatment (4, 5).

Of the numerous clinical trials examined for this study, only 16 of them used combined chemo-radiotherapy and met the following selection criteria:

- cisplatin should be the sole chemotherapeutic agent in combination with radiation, the patients should have unresectable squamous cell carcinomas of the head and neck (stage III or IV) with no recurrent disease or distant metastases, and
- the patients should not have received previous treatment for the same malignancy.

These clinical studies indicate that treatment-related parameters (drug dose, route of administration, delivery time, radiation dose, fractionation type, timing between radiation and drug delivery, overall treatment time) and the disease-

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related parameters (tumour stage, nodal stage, tumour resistance) are crucial to the success of the treatment.

CISPLATIN

Cisplatin (cis-diammine-dichloro-platinum) is a heavy metal complex, with a central platinum atom surrounded by two chlorine atoms and two ammonia molecules. With cisplatin, the chlorine atoms are situated on the same side of the platinum complex (*cis* position). There are five major characteristics that are considered to be responsible for the cytotoxic effects of cisplatin: radiosensitizer—through the inhibition of the repair of potentially lethal damage and sublethal damage—hypoxic cell sensitizer, cell-cycle perturbator, the ability to form DNA adducts and, in addition, the suppression of tumour neovascularization by cisplatin has been identified recently and is under further investigation (6).

Cisplatin as a single therapeutic agent

Cisplatin has the ability to form both intrastrand and interstrand adducts with DNA (7). Although the number of interstrand cross-links is less than 1% of the total adducts (8), Reed & Kohn consider this type of adduction responsible for the cytotoxic effect of cisplatin. The *trans* isomer (with the chlorine atoms located across the platinum complex), transplatin, has proved to be inactive on tumour cells (8) as it cannot be linked interstrand to the DNA, but can form intrastrand adducts.

The schedules and results for a number of different trials in which cisplatin was administered alone are presented in Table 1. Although some of these trials (9–12) have shown cisplatin to be equally effective as radiotherapy alone, the trials were undertaken primarily with recurrent diseases and the expected results were poorer than those for some previously untreated tumours. This has led to the administration of this platinum compound mainly for palliation.

Cisplatin has been delivered either in the range 80–120 mg/m^2 or 20–60 mg/m^2. In Veronesi et al.'s trial (11), the tumour response and normal tissue toxicity were compared after high-dose infusion (120 mg/m^2) given every 3 weeks for 2 cycles and also after low-dose infusion (60 mg/m^2) following the same schedule. While the tumour response was the same, the higher dose resulted in greater toxicity and necessitated more extensive patient hydration. Similar overall responses were achieved by Sako et al. (12) with 15-min infusion of 20 mg/m^2 for 5 days, cycled every 3 weeks to a group of patients, and a high-dose regimen of 120 mg/m^2 every 3 weeks to another group. In contrast, however, toxicity was found to be minimal (9), or moderate and better tolerated (10) when low doses of cisplatin were administered by 24 h infusion. These results are in agreement with the ototoxicity study by Vermorken et al. (13) and suggest that a daily slow infusion of a low-dose is preferable to a bolus, or fast, high-dose administration.

Cisplatin followed by radiotherapy

A phase II study of weekly high-dose cisplatin and radiotherapy delivery given in two separate schedules was conducted by Planting et al. (14) on 59 patients with previously untreated, locally advanced, head and neck tumours. The chemo-treatment time was 6 weeks, with weekly doses of 80 mg/m^2 cisplatin infused over 3 h. Following the administration of cisplatin, 47 patients received conventional radiotherapy with 1.8–2 Gy daily doses for a further 6–7 weeks. In as much as neither chemotherapy alone nor radiotherapy alone resulted in significant improvements in survival, the endpoints of this concomitant schedule study were also inferior (32 weeks' progression-free survival and 56 weeks' overall survival) to those reported for the concurrent regimens (Table 2).

The interplay of cisplatin and radiation

Cisplatin has properties suggesting the suitability of combining the drug with radiation (15–18).

In vivo studies (15) examining the effects of combined cisplatin-radiation treatment concluded that the primary interaction between the two agents is the cisplatin-induced increased oxygenation of the hypoxic cells. Based on these experimental results, Yan & Durand (15) suggested that cisplatin should be delivered before, rather than after, irradiation.

The chemical reactivity of cisplatin is determined by the chloride groups situated in the *cis*-position of the platinum complex. Cisplatin's radiosensitizing property is due to its affinity with the thermalized electron created by radiation-induced ionization within the DNA molecule. This affinity obstructs the recombination with the positive whole (7) and may lead to irreparable damage to the DNA (16). This inhibition of sublethal damage repair (SLDR) by cisplatin was demonstrated by experiments on oxic mammalian cells (17) and also by experiments conducted on human squamous cell carcinomas of the head and neck (18).

Cisplatin also has the ability to arrest cells in the G2 phase of the cell cycle and, possibly, to induce their death. For concentrations greater than 2 μg/mL, cisplatin suppresses the DNA synthesis of L1210/0 cells (19–21). After 4 days, the cell membrane integrity is lost, leading to cell death. For lower concentrations of cisplatin, the cells are just transiently blocked in the G2 phase, for up to 48 h, and after this period they regain their viability. This same DNA degradation process is thought to occur in human tumour cells, as the concentrations used in clinical chemotherapy are significantly higher than those in the above in vitro experiments.

It is difficult to appreciate which property is predominant, as some properties are more strongly manifested in bacterial systems (free radical scavenging) and others in cultured mammalian cells (SLDR inhibition) (17). Whether

Table 1

Cisplatin as a single agent for advanced head and neck cancers

Trial or study	No. of patients & patient selection	Treatment type	Chemotherapy schedule	Endpoints		
				Complete response[1]	Partial and/ or overall response	Toxicity (side effects)
Jacobs et al. (9) Phase II	18 Advanced SCC H&N	24-h infusion	80 mg/m^2 every 3 wks	5.5%	PR[2]–33% Overall response 72%	Minimal toxicity: renal 6% Haematologic: 9% Gastrointestinal: 76%
Creagan et al. (10) Phase II	33 Advanced SCC H&N (oral cavity, paranasal sinus, larynx, pharynx,)	24-h infusion	90 mg/m^2/24 h every 3 to 4 wks; intravenously (IV)	–	OR 12% with the duration between 15 and 56 wks	Gastrointestinal, haematologic moderate to severe nausea & vomiting
Sako et al. (12) Phase III	30 Advanced SCC H&N	High-dose (HD) versus low-dose (LD) cisplatin	HD: 120 mg/m^2 in 15 min LD: 20 mg/m^2 in 15 min every 3 wks in 6 cycles	HD: 13% LD: 6.6%	OR: HD: 33% LD: 26.6%	Significant gastrointestinal toxicity—almost all patients; renal toxicity: HD: 66.6%, LD: 58%; ototoxicity with high-frequency hearing loss: HD: 87%, LD: 47%
Veronesi et al. (11) Phase III (randomized study)	62 Advanced SCC H&N (III & IV) (oral cavity, oropharynx, hypopharynx, rhinopharynx)	High-dose (HD) versus low-dose (LD) cisplatin	HD (33 pts) 120 mg/ m^2 IV infusion for 30–45 min LD (29 patients) 60 mg/m^2 IV for 30–45 min every 3 wks for 2 cycles	Insignificant (HD) & zero (LD)	PR: HD: 16.1% PR: LD: 17.8% Median survival 34 wks	Tolerable toxicity HD more severe vomiting but no significant differences in rest

WHO definitions for response evaluation:
[1]Complete response (CR) of a tumour is considered to be the complete clinical disappearance of the tumour, determined by two observations not less than 4 weeks apart.
[2]Partial response (PR) considered as at least 50% disappearance of the tumour, determined by two observations not less than 4 weeks apart.
Abbreviations: SCC H&N = squamous cell carcinoma of the head and neck; HD = high dose (cisplatin); LD = low dose (cisplatin); OR = overall response; min = minutes; h = hours; wks = weeks; mo = months; yrs = years.

the same characteristics are evident for humans remains one of the open questions in combined modality treatment.

Schedules for concurrent cisplatin radiotherapy

Table 2 is a compendium of the limited number of trials and studies on combined cisplatin-radiation that satisfy the previously described selection criteria. The table includes the general regimen for each trial, showing separately the schedules for radiotherapy and cisplatin. Treatment endpoints including complete response, partial and/or overall response and normal tissue toxicity are also tabulated. The sites of cancer were mainly the oral cavity, oropharynx, larynx or hypopharynx, with some trials including nasopharyngeal cancers as well.

Taking into consideration that every patient had advanced disease, most of the above trials and studies had positive results, both in terms of complete response and long-term benefit. Owing to the high toxicity of cisplatin, the side effects were mainly anticipated, although in some trials the complications exceeded the expectations (22, 31). In other cases, interruptions in treatment were necessary because of excessive toxicity (3, 4, 23).

The majority of studies had adopted either daily or weekly cisplatin combined with either conventional or hyperfractionated radiotherapy, keeping a constant chemo- and radiation dose administration regimen throughout the treatment. However, one regimen was developed (24) whereby the schedule was adjusted to take into consideration the tumour proliferation that occurs after approximately 4 weeks of therapy. The treatment was started with conventional radiotherapy with concomitant cisplatin and continued for 4 weeks, followed by another 2 weeks, with radiation twice a day, almost doubling the radiation dose (1.8 Gy/fraction for 4 weeks and 1.8 Gy/fraction—morning and 1.6 Gy/fraction—night for the last 2 weeks). With this schedule, the complete response of 64% was as high as that

Table 2

Cisplatin/radiotherapy schedules for head and neck cancer

Trial or study	No. of patients and patient selection	Chemotherapy schedule	Radiotherapy schedule	Total dose CT	Total dose RT	Endpoints		
						Complete response	Partial and/or overall response	Toxicity (side effects)
Clamon et al. (22) Phase I	14 Stage III & IV all sites, no nasopharynx	1–3 mg/m^2/day	1.1 Gy twice a day	35–105 mg/m^2	70.4–75.9 Gy	21%	PR: 64%	Severe toxicities; central nervous system toxicity became dose-limiting
Leipzig (38) Phase II	14 Advanced SCC H&N	15 mg/m^2 IV d. 1– > 5 d. 21– > 25 0.2–2 h before RT	Conventional RT 6–7 wks	150 mg/m^2	60–66 Gy	78.5%	18 wks without evidence of recurrence	Renal toxicity (1 patient died from renal failure); rare nausea
Al-Sarraf et al. (23) (RTOG study) updated by Marcial et al. (26) Phase II (with 2 control arms) RTOG 81-17 study	124 22% of patients nasopharyngeal	100 mg/m^2 rapid IV bolus every 3 wks, on days 1, 22 & 43	1.8–2 Gy/day 5 days/week 7 wks	300 mg/m^2	66–73.8 Gy	71% (best response: 89% nasopharynx worst response: 37% hypopharynx	PR: 30% 60% patients finished the complete treatment; survival rate: 1 yr: 68% 4 yrs: 34% (all patients) 4 yrs: 12% (when nasopharynx is excluded)	Severe toxicities: haematologic: 19%; stomatitis: 31%; renal: 6%; 1 patient-renal failure; The adequate CRT was delivered in 58% of patients
Harrison et al. (24) Phase II (prospective study)	24 12.5% nasopharyngeal patients (stage IV)	100 mg/m^2 on days 1 & 22	1.8 Gy/day for 4 wks followed by BID-RT for 2 wks: am fraction: 1.8 Gy given to the entire area of risk & p.m. fraction: 1.6 Gy given to the gross disease alone. Fractions were separated by 4–6 h. Total: 6 wks	200 mg/m^2	70 Gy (1.8 Gy for 4 wks + 3.4 Gy for 2 wks = 36 Gy+ 34 Gy)	64% No different results when excluding nasopharynx	PR: 32%; Local disease-free survival at 1 yr–56%; overall survival at 1 yr–69%	Well-tolerated treatment despite its intensity; 1 treatment related death: 100% pts–mucositis; 17% pts did not receive their day 22 cisplatin because of decreased renal function
Fontanesi et al. (36) Phase II	30 Stage III & IV all sites	100 mg/m^2 IV infusion over 6 h on days 1, 21 & 42	1.11 Gy twice a day, 4–6 h interfractions initiated within 12 h of the first course of cisplatin 6–8 wks	300 mg/m^2	60–76.35Gy	89%	Survival without evidence of disease at 19 mo–66%	Acceptable toxicity; 1 death from renal failure; 23% patients–severe xerostomia; significant weight-loss (4%–20% of body weight)

Table 2 (*Continued*)

Trial or study	No. of patients and patient selection	Chemotherapy schedule	Radiotherapy schedule	Total dose CT	Total dose RT	Endpoints		
						Complete response	Partial and/ or overall response	Toxicity (side effects)
Gasparini et al. (29) Phase II	35 Stage II (unresectable), III & IV all sites	80 mg/m^2 IV infusion of 30 min, 2 h after the beginning of RT, every 3 wks: days 1, 21 & 42	2Gy/day 6–8 wks	240 mg/ m^2	60–70Gy	75%	PR: 25% Estimated 1 yr survival–58%; estimated 2 yrs survival–46%;	Moderate renal & haematologic toxicities (< = grade2); 87% patients-stomatitis (37% severe stomatitis-grade4, which led to a split of 10–15 days after 30 Gy of RT for 34% patients; these patients did not receive the last course of CT).
Glaser et al. (30) Phase II	36 All sites (oral cavity, oropharynx, larynx, hypopharynx; no nasopharyngeal	Single weekly dose: 35 mg/m^2 over 1 h, 3–4 h before irradiation	2 Gy daily over 6 wks	210 mg/ m^2	60 Gy	75%	PR: 25% Disease-free survival: 64% at 1 yr; 52% at 2 yrs; Overall survival: 81% at 1 yr; 47% at 2 yrs	No renal toxicity; well-tolerated treatment; 86% patients received the full schedule of weekly cisplatin
Fountzilas et al. (28) Phase II	48 16% nasopharyngeal	100 mg/ m^2 on days 2, 22 & 42	1.8 Gy/day 5 days/wk 7 wks	300 mg/ m^2	70 Gy	72% (87.5% nasopharynx87.5% oropharynx; 79% larynx) less for other sites	PR 10%; Survival after 4 yrs 34%	No severe nephrotoxicity; 80% patients received the total dose; more than 50% patients had considerable weight loss; quite serious side effects
Arias et al. (27) Phase II (pilot study)	40 Stages III & IV 7.5% nasopharyngeal	20 mg/m^2/day days 1– > 5 in continuous perfusion	1.6 Gy twice a day; 4–6 h interval; 2+2 wks with 2 wks gap	100 mg/ m^2	64–67.2 Gy (100% nasopharynx 100% larynx)	92.5%	2 yrs overall survival–64%; 3 yrs overall survival–47%; 2 yrs local control–65%	The protocol was completed for all patients; mucositis–75% No other severe acute toxicities; late toxicity–xerostomia–45%
Robbins et al. (31) 1997 Phase II (RADPLAT protocol-Memphis experiment)	60 Stage III & IV all sites, no nasopharynx	150 mg/m^2 weekly (days 1, 8, 15 & 22), intra-arterial rapid delivery 3–5 min	1.8–2Gy once daily 5 days/wk	600 mg/ m^2	66–74 Gy 7–8 wks	75% (91% primary site; 67% lymph nodes)	85% completion rate; 1 yr overall survival 67%; 3 yrs overall survival 60%	42% patients grade III–IV toxicity; 25% patients died of disease

Table 2 (*Continued*)

Trial or study	No. of patients and patient selection	Chemotherapy schedule	Radiotherapy schedule	Total dose CT	Total dose RT	Endpoints		
						Complete response	Partial and/or overall response	Toxicity (side effects)
Bachaud et al. (37) Phase II	11 (curative intent) Stage IV oropharynx & hypopharynx	5–7 mg/m^2/day	1.8 Gy/day 8 wks	200–280 mg/m^2	72 Gy	66%	PR-16%; Overall survival–16 mo; 33% patients disease-free for 12–33 mo	Haematologic toxicity was the dose-limiting factor (at 7 mg/m^2/day, none of the patients completed the chemo protocol); There was no nephro-, oto-, or neurotoxicity
Choi et al. (4) Phase II (prospective study)	21 17-curative intent (59% nasopharynx); 4-palliative intent	5–10 mg/m^2/day (continuous infusion) 3 courses of 2 wks (1 wk break between)	1.2–1.25 Gy twice a day (4–6 h interval) 3 courses of 2 wks (1 wk break between)	150–300 mg/m^2	64.8–70.8 Gy	94%	47% patients survived > 3 yrs	Acceptable acute reactions despite concomitant infusion
Huguenin et al. (32) Phase II (pilot study)	64 Stage III & IV all sites, no nasopharynx	20 mg/m^2/day 5 days in wks 1 & 5	1.2 Gy twice a day-6-h interval	200 mg/m^2	74.4 Gy	LC–74%	Local control at 5 yrs–74%; overall survival at 5 yrs–37%	27% patients > = grade 3 toxicity; 50% patients with permanent xerostomy
Serin et al. (33) Phase II	70 Advanced nasopharynx	30 mg/m^2/wk	Conventional RT	180–210 mg/m^2	60–70 Gy	CR-locoregional 90% patients	Overall survival at 3 yrs–63%; locoregional failure-free survival at 3 yrs–79%	14% patients grade 3 toxicity
Jeremic et al. (3) Phase III	53 RT 53 RT+cisplatin Stage III & IV all sites nasopharynx: 11%–RT group 9%–CRT group	6 mg/m^2/day IV bolus 30 min before irradiation	1.8–2Gy daily 5 days/wk 7–7.5 wks	210–225 mg/m^2 (7–7.5 wks)	70 Gy	CRT 72% RT 38%	5-yr survival CRT 32% RT 18%	CRT patients had more treatment interruptions than RT patients owing to acute toxicity (9% versus 4%) Overall, the differences in toxicity were not significant

Table 2 (*Continued*)

Trial or study	No. of patients and patient selection	Chemotherapy schedule	Radiotherapy schedule	Total dose CT	Total dose RT	Endpoints		
						Complete response	Partial and/ or overall response	Toxicity (side effects)
Jeremic et al. (5) Phase III (prospective randomized trial)	65 Stage III & IV all sites, 10% nasopharynx	6 mg/m^2 IV bolus 3–4 h after the first RT fraction	1.1 Gy twice a day, 4.5–6 h interfractions	210 mg/ m^2	77 Gy 7 wks	75%	Survival at 2 yrs–68%; survival at 5 yrs–46%; locoregional progression-free survival at 5 yrs–50%; distant metastasis-free survival at 5 yrs–86%	14% patients > 10% weight loss; 11% patients–treatment interruptions because of acute toxicity; 5% –nephrotoxicity; 12%–leukopenia; 25% –oesophagitis; 49% –stomatitis

Abbreviations: CT = chemotherapy; RT = radiotherapy; CRT = chemoradiotherapy; CR = complete response; PR = partial response.

in other trials with less advanced disease (RTOG group (25)).

Examination of the endpoints in Table 2 indicates that there are many trials with similar responses (complete response between 70% and 78%) (3, 5, 23, 26–31, 38) even though the treatment protocols are different. Both conventional and hyperfractionated radiotherapies were used with similar results and weekly and daily cisplatin administration were also comparable. However, as illustrated in some studies, the response rates may not be the best predictors of treatment efficacy. For example, with weekly delivery of high-dose cisplatin and conventional radiotherapy, Fountzilas et al. (28) achieved a complete response of 72%, identical to the response rate reached by Jeremic et al. (3) with daily low-dose cisplatin. Similarly, Gasparini et al. (29) and Glaser et al. (30) both had a 75% complete response in their studies, using conventional radiotherapy and a single weekly dose of cisplatin, with the same patient selection. In Gasparini's schedule, cisplatin was administered 2 h after radiotherapy and in Glaser's protocol, 3–4 h before irradiation. In two different studies, using the same administration for the drug but different schedules for the radiation, Jeremic et al. (3, 5) completed the treatments with similar results: 72% complete response when conventional radiotherapy was used and 75% complete response with hyperfractionation. Furthermore, Robbins et al. (31) undertook a phase II study in which 85% of the patients completed a targeted supradose cisplatin and concurrent radiotherapy protocol (called the RADPLAT protocol), using intra-arterial delivery. The complete response for this study was 75%, as in many other intravenous trials. However, the 3-year overall survival of 60% was significantly higher than the 47% figure reported by Choi et al. (4) although they had an initial complete response of 94% (mainly with nasopharyngeal patients). This indicates that the tumour response is not necessarily the most relevant endpoint. Robbins et al. (31) went on to explain that rapidly responding tumours might undergo rapid repopulation while slower regressing tumours may be more sensitive to therapy with regard to their future proliferation.

Locoregional control has been shown to be a more accurate indicator of the long-term tumour control than complete response (5, 32, 33). Huguenin et al. (32), using a hyperfractionated radiation regimen with simultaneous cisplatin, achieved a 74% local control at 5 years. A similarly good result was obtained by Serin et al. (33), with 90% of patients having a complete locoregional response, the locoregional failure-free survival at 3 years being 79%. However, patient selection could be the reason for the high response rate in Serin's phase II study, as all patients presented with nasopharyngeal cancer, though in locally advanced stages. With a hyperfractionated radiation given concurrently with daily low-dose cisplatin) Jeremic et al. (5) achieved 5-year locoregional progression-free survival in 50% of the patients.

Toxicity associated with combined treatment schedules

It is essential in correctly defining the endpoints that the toxicities of the different schedules are also taken into account. Most of the studies in Table 2 used the Common Toxicity Criteria adopted by the National Cancer Institute (34). However, in a recent article, Trotti (35) underlined the fact that, in some cases, differentiating between the various grades of toxicity is difficult even for experienced examiners.

The goal therefore is still to assure greater data accuracy through standardization of the collected data.

One of the organs most affected by cisplatin administration is the kidney. For every schedule using high-dose cisplatin, either combined with conventional fractionated or hyperfractionated radiotherapy, the nephrotoxicity was substantial (grade III or IV), even though, overall, the treatments were well tolerated. All of the patients who suffered renal failure or nephrotoxicity-related death had participated in trials that used high doses of cisplatin (100mg/m^2) every second or third week (23, 24, 26, 36). Other studies with lower renal toxicity presented other significant side effects. Gasparini et al. (29) could not deliver a whole course of chemotherapy for 34% of the patients because of high-grade stomatitis. Fountzilas et al. (28) similarly had to deal with considerable weight loss in half of his patients.

Robbins et al. (31) conducted a trial in which the selected drug route was intra-arterial rather than intravenous, with the aim of delivering a higher concentration of drug (150 mg/m^2) directly into the tumour and sparing the normal tissues. However, overall, 42% of patients still had grade III or IV toxicities.

Daily low-dose cisplatin has been better tolerated in several studies (3, 5, 37, 38). Choi et al. (4) have also used the daily low-dose cisplatin schedule, and planned interruptions during the treatment to prevent excessive toxicity. As a result, there were no renal failures or nephrotoxicity-related deaths.

Various late toxicity effects have been reported in a few trials. Marcial et al. (26) evaluated the late toxicities in the 72% of treated patients that achieved a complete response, reporting 3% with necrosis, 4% with fibrosis and 8% with other toxicities (otitis, paresthesia, dental caries). Choi et al. (4) reported minimal late toxicity consisting of mild fibrosis, xerostomia, otitis and dental caries with no severe toxicities being reported at follow-up. Late high-grade toxicity was observed in Jeremic et al.'s (5) trial where xerostomia was manifested in 22% of the patients and subcutaneous toxicities in 12% of the patients after receiving combined treatment.

CHEMORESISTANCE AND RADIORESISTANCE

Many tumours have a high initial response to chemotherapy, which diminishes or disappears during the course of therapy (39) (chemoresistance) thus representing an obstruction in reaching long-term remission or cure (40). There are various causes of chemoresistance and these are still under investigation. The drug type, the administered dose and the timing of the drug delivery are elements that can influence the tumour response during the treatment period (41). Tumour chemoresistance is indicated by decreased drug uptake and increased DNA repair (42, 43), which can be linked to the low doses of cisplatin delivered.

Robbins et al. (44) clinically investigated whether a drug-resistant tumour remains resistant even for high doses of cisplatin through a tenfold increase in the administered dose. The doses used in this trial ranged from 32.5 to 200 mg/m^2 per week, and to overcome toxicity, cisplatin was delivered by intra-arterial infusion with simultaneous intravenous administration of sodium thiosulphate as a neutralizing agent. The tenfold increase in drug dose ("decadose") showed a significant improvement in overcoming drug resistance, the results being positive even for recurrent cancers.

In experimental studies with substances such as LipoAmph B (a liposomal preparation of Amphotericin B) (45) it was possible to increase the platinum intake by the tumour compared to the surrounding tissues, when administered concurrently with cisplatin, thus increasing cisplatin toxicity to the tumour. The study was completed on a head and neck squamous cell carcinoma line and synergism between the two drugs was indicated by an enhancement in cytotoxicity from 35% to 60%.

In clinical radiotherapy, it has been demonstrated that various tumours have the ability to regrow within the irradiated region independently of their regression rate (46). This phenomenon leads to tumour radioresistance and is multifactor dependent. Peters et al. (46) examined four main causes of clinical radioresistance: tumour-related factors (hypoxia, the number of clonogenic cells, tumour kinetics), host-related factors (defence, the volume effect, dose-limiting normal tissue), technical factors (geographic miss, errors in dose delivery) and probabilistic radioresistance. The tumour-related factors are common for both drug resistance and radioresistance. The so-called cross-resistance is one of the most debated problems in combined treatment, as many tumours resistant to one agent readily become resistant to the others. Unfortunately, cisplatin-resistant head and neck tumours are generally radioresistant, too (47). Hypoxia plays an important role in tumour resistance, to both cisplatin and radiation. Novel hypoxic cell sensitizers, e.g. tirapazamine, have improved the cytotoxic effect of cisplatin and radiation when administered concurrently (48). Dorie et al. (49) have measured the DNA damage mediated by tirapazamine in hypoxic head and neck tumours, concluding that the drug is activated by the poorly oxygenated environment, leading to radioresistant cell kill.

Furthermore, to overcome radioresistance caused by hypoxia, Peters et al. (50) developed a specific drug administration schedule that differed from the other schedules in the drug timing. They supported the idea that drug delivery should be deferred until the final part of the treatment 'as late intensification'.

Theory versus practice

Table 3 indicates that, in the past, treatment schedules have not been fully in accordance with the clinical, biochemical and physical indicators (51–54). Nevertheless, when there is greater correlation between the treatment regimen and these indicators, the tendency is towards an improved outcome, as can be seen from Jeremic et al.'s recent trial (5).

DISCUSSION

Since Rosenberg's initial discovery, cisplatin has progressed from its early use in isolation in the 1970s to a variety of initial forms of combined chemo-radiotherapy in the subsequent decades. While in the 1980s and early 1990s most of the schedules used high-dose weekly cisplatin administration (23, 24, 26, 28, 29, 36), in the mid- to late-1990s daily low-dose infusions were introduced (3–5, 37) and outcomes have continuously improved.

The cytotoxic effects of cisplatin are attributed to the ability of the drug to form interstrand adducts with cell DNA, to inhibit DNA synthesis resulting in cell-cycle arrest and, more recently, to its inhibition of neovascularization.

While these effects are independent of other mediators, cisplatin can also work in cooperation with ionizing radiation through its affinity with free electrons resulting in the inhibition of SLDR, and increased oxygenation of hypoxic cells resulting in increased radiosensitivity. For this cooperation to be achieved, cisplatin needs to be delivered prior to the application of radiation. Furthermore, the clearance time of cisplatin (24 h) requires ongoing administration of cisplatin to sustain the cooperation. Through daily drug administration, all the properties of cisplatin are exploited and this is supported by the superior results obtained in trials using daily administration of cisplatin compared with weekly drug delivery.

The dose-limiting toxicities for cisplatin must also be taken into consideration. Renal and haematologic toxicities, and also stomatitis, were the most frequently reported dose-limiting factors. In a number of trials, a daily cisplatin dose of 6 mg/m^2 was considered to be the upper limit if the higher-grade toxicities were to be avoided (3, 5, 37). Even though cisplatin is more toxic than many other anticancer drugs, it has the advantage that its toxicity does not overlap with the radiation-produced side effects. Furthermore, cisplatin-induced renal and haematologic toxicities can be overcome by daily low-dose infusion of the drug and the use of antiemetics and hydration to reduce nephrotoxicity. Inevitable side effects, e.g. stomatitis and xerostomia, disappear after the completion of treatment.

As with drug-dose fractionation (daily administration), the use of accelerated and/or hyper-fractionated radiotherapy has led to better outcomes than those with conventional radiation treatment. Tumour resistance to chemo/radiotherapy is one of the reasons for treatment failure. Radioresistance is reduced by hyperfractionation and accelerated radiotherapy. While this is still an area for further investigation, this response may reflect the accelerated cell growth ('kick-off') post-initiation of treatment with head and neck cancers. Similarly, chemoresistance can be overcome by increasing the drug dose but the disadvantage of increasing the drug dose is the increase in toxicity. Other alternatives are to use treatment combinations or to administer substances, such as LipoAmph B, that are able to increase the platinum intake by the tumour. However, normal tissue toxicity must be considered when discussing long-term, disease-free survival or locoregional control.

Table 3

Theory versus practice

Theory (based on in vitro studies)	Clinical practice
The treatment time for HNC should be kept as short as possible because of the rapid repopulation after RT (51). The recommended treatment period is 5 weeks (52).	All treatments discussed in the present paper lasted for more than 6 weeks and up to 8 weeks.
Because of the HN tumour proliferation after beginning radiotherapy, it is not recommended to interrupt the treatment (53).	Many treatments were interrupted for 1–2 weeks (for one or more cycles) because of different toxicities, some interruptions being programmed (4, 27) but some not (29).
The formation of DNA adducts is a fast process (approximately 3.5 h) and lasts up to 24 h after 1-hour exposure to cisplatin. After this period, most of the DNA adducts have disappeared, which can explain the total absence of an additive effect when cisplatin is given 24 h before irradiation (results from in vitro experiments on a tumour spheroid, cultured from an HNC patient's tumour) (56).	More than half of the schedules contain high-dose weekly cisplatin, in 2–3 cycles, which is toxic to the normal tissue rather than effective on tumour cells (23, 24, 26, 28, 29, 31, 36).
Many tumours have the capacity to increase their rate of clonogenic cell replication significantly above pretreatment levels during the course of radiotherapy (50).	With the exception of Harrison et al.'s trial (24), which takes into account that after approximately 30 days HN tumours proliferate more rapidly than before (adjusted schedule for this case), none of the other studies or trials use such adjustments, or different doses for that particular part of the treatment.

At present, there is no optimal schedule for treating head and neck cancer and the most efficient and least toxic cisplatin dose has still not been established (55). However, Jeremic's phase III trial (5) comprising patients with advanced head and neck cancers and using hyperfractionated radiotherapy and concurrent low-dose daily cisplatin achieved substantial tumour responses with acceptable normal tissue toxicities, and the available data make a good starting-point for further trials.

The optimal timing between drug delivery and radiotherapy remains to be resolved by larger and more conclusive trials. Furthermore, the results of clinical trials will be improved by a better understanding of the underlying mechanisms by which chemotherapy enhances the effectiveness of radiation. The radiobiological properties of drug-radiation interaction are examined through upcoming models. The present review has laid the foundation for a computerized simulation of treatment schedules for a virtual head and neck tumour (56) that will serve as a basis for temporal studies of combined chemo-radiotherapy.

CONCLUSIONS

The aim of combined chemo-radiotherapy treatment is to reach a higher therapeutic ratio than that with single-agent therapy through both a better tumour response and reduced normal tissue damage. In the present paper we have reviewed a selected number of trials on unresectable squamous cell carcinoma of the head and neck with cisplatin used as a single chemotherapeutic agent with and without irradiation. Treatment regimens that correlate better with the pharmacokinetics and the radiobiological properties of the therapeutic agents resulted in better outcomes, although there is still a dearth of large, conclusive, controlled and randomized trials.

There are indications that optimization of the treatment can be improved through further study and modelling of the pharmacokinetic and radiobiological interactions.

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