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European Journal of Cancer 38 (2002) 1478–1489

European Journal of Cancer

www.ejconline.com

Use of high-dose cytarabine to enhance cisplatin cytotoxicity—effects on the response and overall survival rates of advanced head and neck cancer patients

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Received 24 April 2001; received in revised form 30 January 2002; accepted 25 February 2002

Abstract

It has been reported that cytarabine, acting by at least two different mechanisms, enhances the cytotoxic effect of cisplatin in *in vitro* systems. The aim of this open, prospective, randomised study was to estimate the eventual benefits from the inclusion of high-dose cytarabine in the cisplatin-5-fluorouracil (5-FU) regimen as first-line treatment of patients with advanced head and neck cancer. The study recruited successive patients with unresectable grade I/II head and neck cancer who were not suitable for irradiation treatment (T any N3 or T4 N2C), metastatic or previously irradiated. All patients gave their informed consent. A joint ear, nose and throat (ENT) oncological committee performed the selection. A total of 170 patients were included in the study. Patients randomised to arm A were given 1000 mg/m^2 cytarabine on day 1 preceding for 6 h cisplatin infusion, 30 mg/m^2/24 h cisplatin intravenous (i.v.) bolus days 1–4 and 1000 mg/m^2/24 h 5-FU in a 4-h infusion on days 1–4. Patients in arm B were given cisplatin and 5-FU in the same dosage and schedule as in arm A. Additional irradiation ± surgery was performed if and when feasible. Patients in both arms were well balanced with regard to clinical variables. The following results were obtained: Arm A: 84 patients were included, 74 were evaluable for activity; Response: complete response (CR) 8 (11%), partial response (PR) 40 (54%), stable disease (SD) 11 (15%), progressive disease (PD) 15 (20%). The overall response rate (RR) based on the evaluable patients was 48/74 (65%, 95% confidence interval (CI) 54–75%); The RR based on an intent-to-treat analysis was 57%, 95% CI 47–67%; Median survival was 13 months; There were 50 episodes of granulocytopenia grade IV and 15 of febrile neutropenia per 316 cycles. Arm B: 86 patients were included, 80 were evaluable for activity; Response: CR 7 (9%), PR 29 (36%), SD 10 (12.5%), PD 34 (42.5%); The overall RR based on the evaluable patients was 36/80 (45%, 95% CI 35–56%); The RR based on an intent-to-treat analysis was 42%, 95% CI 32–52%; Median survival was 8 months; There were 14 episodes of granulocytopenia grade IV and 7 febrile neutropenias per 324 cycles. The RR was significantly higher in arm A ($P = 0.013$), power (one-sided) 80%. The proportion of patients from the appropriate subset who achieved a clinical response making additional treatment feasible was higher in arm A ($P = 0.00015$), as well as the proportion of patients with a performance status 2 + 3 achieving a response ($P < 0.0001$). Using the Log-rank test, patients from arm A achieved a significantly longer survival ($P = 0.009$), with the probability of survival at 12 months of 0.58 for patients in arm A and 0.28 for patients in arm B. Grade IV granulocytopenia and thrombocytopenia were more frequent in arm A. Due to its haematological side-effects, cytarabine might not be the ideal drug to modulate the cytotoxicity of cisplatin. However, other modulators of its activity could be of interest for further studies in head and neck cancer patients.

Keywords: Cytarabine; Cisplatin; 5-FU; Head and neck cancer; Chemotherapy

1. Introduction

Cisplatin is one of the most active drugs in head and neck cancer, producing response rates from 27 to 40% in chemotherapy-naive patients [1,2]. The cisplatin-infusional 5-fluorouracil (5-FU) regimens are considered as standard chemotherapy in both the neoadjuvant and palliative setting for patients with advanced head and neck cancer [3,4] The variations in response rates (RRs) obtained with this regimen (35–70%) are likely to depend on several factors, including patient selection [5,6]. Nevertheless, there are a significant

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0959-8049/02/$ - see front matter
PII: S0959-8049(02)00112-0

proportion of patients who either display primary resistance to cisplatin-containing regimens or who develop resistance during treatment.

Clinical tumour resistance to cisplatin is partly related to the activation of enzymatic repair mechanisms that are responsible for the deletion of cisplatin-attacked DNA segments [7]. Cytarabine, a drug known to be inactive in head and neck cancer, when incorporated into *de novo* synthesised DNA segments, has been shown to be able to modulate the activity of other cytotoxic drugs. Cytarabine has been reported to produce cytotoxic synergy with cisplatin *in vitro* and modifications in cisplatin-induced DNA cross-linking; the drug has also been shown to inhibit the DNA enzymatic repair system that is responsible for the resistance to cisplatin. Thus, acting by two different mechanisms, cytarabine can enhance the cytotoxic effects of cisplatin *in vitro* [8]. The cytarabine-dependent enhancement of cisplatin antitumour activity on several different tumour cell lines, including those from human head and neck cancer, was evidenced only when cells were treated with the drug at least two hours before cisplatin [9]. The same study, apart from demonstrating a time-dependent enhancement, provided data that cytarabine-induced modulation of cisplatin antitumour activity was also dose-dependent [9]. Taken together, all these findings suggested that cytarabine modulates the repair of platinum–DNA adducts at clinically achievable concentrations [10].

Clinical studies of the enhancement of cisplatin-induced antitumour activity by low dose continuous infusional cytarabine in tumour types that are resistant to cisplatin such as pancreatic cancer and pretreated breast cancer, resulted in no significant activity [11,12]. However, in other solid tumours, 12-h continuous infusional cytarabine concurrent with hydroxyurea and preceding 100 mg/m^2 cisplatin induced a response in 3 of 8 cisplatin-pretreated patients [13]. The cytarabine-hydroxyurea-cisplatin combination, used to treat 51 patients with recurrent head and neck cancer, achieved a response rate of 45%. The dosages were 35 mg/m^2×4 days for cytarabine and 25 mg/m^2×4 days for cisplatin and granulocytopenia was the factor limiting the continuation of chemotherapy in responding patients [14]. Continuous infusion of 30 mg/m^2/day cytarabine for 72 h with cisplatin 30 mg/m^2 at hours 16, 36 and 60 in the same category of patients achieved "activity comparable to that of other cisplatin-containing regimens, but excessive haematological toxicity" [15]. Thus, it seems that repeated or continuous infusional low dose cytarabine administration was, in most studies, associated with a significant and troublesome haematological toxicity.

From experience with haematological malignancies, it is known that short infusional high-dose cytarabine has an acceptable haematological toxicity [16]. In order to explore the dose-dependent synergy between the two drugs, two phase II trials have been conducted, but with drug scheduling that was not quite consistent with the *in vitro* data. In one study, 3 g/m^2 cytarabine and 100 mg/m^2 cisplatin failed to improve the response rate (RR) achieved with cisplatin treatment [17]. The other schedule, although 500–4000 mg/m^2 cytarabine was administered after cisplatin, appeared more active than cisplatin alone and, in addition, was haematologically well tolerated [18]. In our previous study with 1000 mg/m^2 cytarabine applied before 130 mg/m^2 cisplatin per cycle, we obtained two complete responses (CRs) and one partial response (PR) in 14 patients refractory to cisplatin at the same dosage and with World Health Organization (WHO) grade IV toxicity for granulocytes registered in only 1 patient [19].

On the basis of these results, the possibility of including cytarabine in a cisplatin-5-FU regimen as first-line treatment appeared possible. The present randomised study aimed to examine whether the enhancement of cisplatin cytotoxicity with short infusional high-dose cytarabine adds clinical activity to the cisplatin–5-FU regimen for advanced head and neck cancer. The subpopulation of patients which appeared most suitable for this study were those with either high volume disease or with recurrent/metastatic head and neck cancer; in this subpopulation, the cisplatin + 5-FU combination in a neoadjuvant approach or in the 'chemotherapy only' setting has only a palliative use with a low prospect of any cure.

2. Patients and methods

2.1. Purpose of the investigation

The purpose of this investigation was to compare cisplatin and 4-h infusional 5-FU with the same regimen, but with the cytotoxicity of cisplatin enhanced by 1 g/m^2 cytarabine in a poor prognostic group of patients with locoregionally advanced or metastatic head and neck cancer. The following factors were analysed; overall response rate, proportion of patients achieving a response making additional treatment modalities feasible (surgery and/or irradiation treatment), overall survival and toxicity.

The study was a monocentric joined study, the initial diagnosis, the interim diagnostic evaluation and surgery all being performed at the Institute for Otorhinolaryngology and Maxilofacial surgery of the Clinical Centre in Belgrade. Chemotherapy and irradiation treatment were performed at the Institute of Oncology and Radiology of Serbia. A joint ear, nose and throat (ENT) committee of the two institutions, which have operated for nearly 40 years, made all of the therapeutic decisions.

2.2. Patients

The patients included in the study had squamous cell carcinoma of nasopharynx, oral cavity, mesopharynx,

hypopharynx or larynx, of histological grade I or II, that is histologically-proven by two experienced pathologists. UCNT (undifferentiated carcinomas of the nasopharynx) were not included. All patients had to be chemotherapy-naïve.

Patients belonged to a arbitrarily defined poor prognostic group, which included:

- Radiotherapy-naïve patients with non-resectable bulky nodal disease, i.e. T any N3 M0 or T4 N2c (fixed, over 5 cm) M0, or
- Patients with metastatic disease, i.e. any T, any N, M1 or
- Patients with non-resectable nodal relapses within a previous irradiation field, i.e. any T, N2c-3, any M.

These patients are unlikely to be cured because of the high-nodal volume disease and have a poor short-term prognosis [20]; the same applies to patients with recurrent or metastatic disease.

Additional criteria for inclusion were:

- Presence of at least one measurable lesion (either nodal or metastatic in parenchymatous organs),
- No previous history of malignant disease, except basal cell carcinoma of the skin,
- No previous active treatment for chronic aethylism and no other psychiatric or neurological disease which could interfere with the patient's compliance or the chemotherapy tolerance,
- No previous loss in body weight of over 15%,
- No trismus which could interfere with swallowing and/or vomiting,
- Absence of oesophageo-tracheal fistula, for patients with carcinoma of the hypopharynx invading the proximal oesophagus,
- No history of congestive heart failure or myocardial infarction and no other cardiac disorder which could interfere with the 5-FU administration,
- Normal hepatic, renal and bone marrow function,
- Performance status 0–3 according to Eastern Cooperative Oncology Group (ECOG) criteria,
- Absence of central nervous system (CNS) metastases,
- Age below 75 years,
- Witnessed oral informed consent.

Since the enrolment of patients started in 1995, the consent procedure was performed in accordance with the 1989 version of the Declaration of Helsinki. Witnessed oral consent of the patients was required for inclusion in the study, as in the 1989 Helsinki declaration written consent was 'preferable', but not mandatory. Witnessed oral informed consent is more suitable to the cultural and educational background of our patients, and was acceptable both to local requirements and to the ethical authorities when they approved this study. Patients who refused enrolment after being given information about the study purpose and prognosis with regard to disease extent were then offered standard chemotherapy, i.e. treatment as in arm B of this study.

2.3. Chemotherapy

Patients were randomised into two arms.

- Arm A: 1000 mg/m^2 cytarabine given at 9.00 in the morning (1-hour infusion), 30 mg/m^2 cisplatin given at 15.00 hours intravenous (i.v.) bolus, 1000 mg/m^2 5-FU, as a 4-h infusion following cisplatin on day 1; then on days 2, 3 and 4 30 mg/m^2/24 h cisplatin and 1000 mg/m^2/24 h 5-FU in a 4-h infusion applied at the same times as on day 1.
- Arm B: 30 mg/m^2/24 h cisplatin and 1000 mg/m^2/24 h 5-FU on days 1–4 applied at the same times and schedule as for arm A.

5-FU was applied as a 4-h infusion following data from previously published studies, claiming a similar activity for the 4-h and the continuous infusion of the drug [21] in head and neck cancer patients.

According to the results of our previous study, i.e. that short infusional high-dose cytarabine (1000 mg/m^2) preceding cisplatin in cisplatin-refractory head and neck cancer patients had a good haematological tolerance and did revert the cisplatin resistance of several patients [19], and given the poor prognosis of the patients that were included in this study, the dosage of 1000 mg/m^2 was incorporated in the regimen of the arm A without a previous dose-finding study.

The intercycle interval was 4 weeks. The next cycle was postponed for 1 week when haematological recovery was incomplete (i.e. granulocytes less than 1.5×10^9/l and platelets less than 100×10^9/l). Dosage modifications were foreseen in three possible situations. When febrile neutropenia, classified as infection grade III, recurred for two consecutive cycles or when grade IV was present during one cycle, the dosage of cytarabine was reduced for 50%. Grade III non-haematological toxicities related to the 5-FU administration, whether associated or not with haematological toxicity, required a 50% reduction of the drug dose. If it was not possible to identify the drug that was responsible for the toxicities the dosage of both cytarabine and 5-FU was reduced up to 50%. Reduction of the cisplatin dosage was foreseen only for slowly reversible nephrotoxicity of grades II/III that was interfering with the start of the next cycle. Any non-haematological grade IV toxicity required chemotherapy withdrawal. It was intended that patients

achieving a CR or a PR should receive up to six treatment cycles, unless the ENT committee thought that further chemotherapy brought no additional benefit for the patient, or until radiotherapy, preceded or not by nodal surgery, became feasible, and this treatment had a better prospect for a clinical benefit than further chemotherapy. Patients achieving a stable disease (SD) received three or four cycles depending on the clinical benefit. All patients with CR, PR and SD were reviewed for the possibility of additional post-chemotherapy treatment modalities. Exclusion from further treatment was foreseen for patients with progressive disease after the second and third cycle, and even after the first if progression was estimated to be 50% or more; these patients received best supportive care. When disease progression was noted following initial stabilisation or response, chemotherapy was withdrawn and patients were reviewed for the possibility of receiving post-chemotherapy treatment modalities.

Supportive treatment was applied, as needed, during and following chemotherapy. 30 mg/m^2/24 h cisplatin was applied with hydration containing 0.9% NaCl and Ringer lactate solutions, sodium and potassium supplementation and forced both osmotic (20% manitol) and saline (furosemide i.v.) diuresis; the drug was applied through the running tube of the 20% manitol infusion. Antiemetics included ondasentron or an ondasentron–dexamethasone combination, as needed. Granulocyte-colony stimulating factor (G-CSF) was applied at the discretion of the treating physicians for either neutropenia grade IV lasting for more than 7 days or for febrile neutropenia not responding to first-line antibiotic treatment (a third-generation cephalosporine and an aminoglycoside).

2.4. Additional post-chemotherapy treatment modalities

Patients with metastatic disease did not receive any additional treatment modality, irrespective of the response that was achieved. Patients with loco-regional disease and relapse within a previous irradiation field were also not considered for additional treatment, except for nodal surgery if they achieved a CR of their primary tumour residue/relapse.

Additional treatment modalities were considered for the irradiation-naive patients with advanced loco-regional disease who fulfilled the criteria for either CR, PR or SD. All patients experiencing a CR received irradiation treatment, 66–70 Gy, 2 Gy per day. Several modalities were considered for patients with SD (which also means a decrease in size of less than 50%) and PR.

For patients with nodal masses of 5 cm or more in diameter that became resectable following chemotherapy, a neck dissection was performed and followed by irradiation treatment. Patients with nodal masses reduced to 3 cm or less in diameter underwent irradiation treatment as described above. A neck dissection was performed and the irradiation treatment continued afterwards for resectable nodes not responding to irradiation at 40 Gy. Patients with resectable nodal masses reduced to 3–5 cm in diameter underwent neck dissection, followed by irradiation treatment; for those with unresectable nodes, irradiation treatment was applied up to a total dose (TD) of 40 Gy and the response was assessed. Responding patients received radical irradiation treatment and those not responding received best supportive care. Patients who were left with unresectable nodal masses over 5 cm in diameter, irrespective whether they were classified as PR, SD, or PD received best supportive care.

No second-line chemotherapy was foreseen.

Irradiation treatment was applied within 6 weeks after the last chemotherapy cycle, i.e. within 2 weeks after the assessment of response to the last chemotherapy cycle; 2 additional weeks were permitted if radiotherapy was preceded by nodal surgery.

2.5. Selection of patients and investigations

Patients who were eligible for the study were selected by a joint committee for malignant diseases of the ENT region of the Institute of Oncology and Radiology of Serbia and the Institute for Otorhynolaryngology and Maxilofacial Surgery of University Clinical Centre in Belgrade, which consisted of at least two ENT surgeons, one radiotherapist and one medical oncologist. Additional opinions were asked for in cases of doubt. Eligibility for the study was confirmed by a signed consensus statement that the patient's tumour was not amenable to surgical treatment, that the prospects of a response to irradiation treatment were poor because of the tumour/nodal bulk, that no nodal surgery prior to eventual irradiation treatment was possible and that there were no general contraindications for chemotherapy.

The initial work-up consisted of anamnesis and clinical examination with a determination of body weight, height and surface area; a complete ENT check-up with epipharyngoscopy or laryngomicroscopy when applicable or indicated by the tumour localisation; the determination of the ECOG performance status; a chest X-ray and abdominal echography, supplemented in suspect cases by a computed tomography (CT) scan; electrocardiogram (ECG) tracing; blood chemistry and complete blood count with a leucocyte differential. Other examinations, including CT scans of the ENT region, were performed according to the clinical setting and expected benefit.

Blood chemistries were performed on days 5 and 10 and the blood counts on days 5, 8 and 10. If a continuous drop in granulocytes and platelet levels was noted, blood counts were repeated every second day

until the nadir. When the nadir value was of toxicity grades III or IV, the blood count was checked daily until recovery.

The blood count and chemistry were repeated before each cycle. All examinations relevant to disease extension were performed after each second cycle (i.e. second, fourth, sixth) and also after the third in order to confirm stable disease (see criteria of evaluation). Nodal disease was followed clinically with supplementation when needed by a CT scan or a cervical echography. The primary tumour response was estimated either by a CT scan or endoscopy depending on the tumour localisation. The response of the metastatic lesions was estimated with chest X-rays (±a CT scan) for lung localisations and abdominal CT scans for metastatic disease in the liver.

2.6. Follow-up

The patients were followed-up on a monthly basis whenever possible for the first 6 months after the completion of treatment and bimonthly thereafter. The dates of death were obtained with the help of the municipal demographical authorities, by contact with the patient's family or through contact with the regional medical centres. The date of death was not available for 7 patients.

2.7. Criteria of evaluation

Patients data, including the whole medical documentation, were presented to members of the ENT committee after the second, third, fourth and sixth cycle (if necessary, even after the first), i.e. before the start of the subsequent cycle. The committee decided on the response category with a signed consensus statement. The decision on whether further chemotherapy should be given was confirmed on every visit and signed by the ENT committee who also made signed consensus statements about post-chemotherapy treatment modalities, including the eventual best supportive care.

Standard WHO criteria were used for the response assessment [22]. Nevertheless, the criteria for SD were slightly modified with regard to the original WHO criteria. In order to classify the patient's response as a SD, the SD criteria must have been met not only following the first and second cycle, but also after the third. This is because progression of less than 25% was classified as SD. The primary tumours and the nodal metastatic lesions in the ENT area may be slowly-growing, and, over a two month interval, the slow evolution of some of these tumours might mimic stable disease. The opinion of the ENT committee was that, for this particular study, stabilisation should be present following the third cycle in order to ascertain a SD with reasonable certainty.

Toxicity was estimated according to the Common Toxicity Criteria-National Cancer Institute (CTC-NCI).

2.8. Statistics

The sample size estimations were done using a presumption that a 25% difference should be present between the two groups in the overall RR. Group sample sizes of 50 and 50 would result in a 40% power to detect this difference with a $P=0.05$, and group sizes of 100 and 100 would result in a power of 95%. Results were checked at regular intervals (interim analyses) for the difference that was obtained and for the power achieved, and the study was stopped when the power for $P=0.05$ reached 80%. Due to a lack of data in the literature on the difference one should expect in terms of survival in this poor prognostic group of patients with the present regimens, the sample size estimation was based on expected difference in the response rates; what was achieved in terms of downstaging and survival was calculated retrospectively.

Randomisation was performed by computer with the random number technique, using a programme to generate random numbers. At the start of the study, a total of 100 numbers were given, 50 for each arm. No stratification was done as all of the groups of patients with advanced head and neck cancer in this study belonged to a poor prognostic category that was fairly uniform [20]. Following the interim evaluation of the first 100 patients, an additional 50 numbers were given to each arm, making a total of 100 for the second part of the randomisation and 200 for the two steps. A new evaluation was performed after the inclusion of 150 patients in the study and randomisation was continued until a power of 80% for $P=0.05$ was reached for the difference in the response rates.

For both treatment arms, response rates and corresponding 95% confidence intervals (CI) were determined, as well as the proportions of patients from the appropriate subset (non-metastatic, not with locoregional relapses within a previous irradiation field) with a clinical response making complementary radiotherapy, preceded or not by surgery, feasible. The Chi square test with appropriate modification was used to analyse the balance of the patient's characteristics of the two arms, to detect the difference between the RRs of the two arms and the difference between the proportions of downstaged patients. Survival curves were estimated by the method of Kaplan and Meier and survival differences with the Log-rank test, with analysis of the Z-values for each month of the follow-up. The differences in the toxicities were assessed by the Chi-square and Fisher tests [23].

3. Results

This study was started in 1995 and the accrual of patients was stopped in December 1998. The analysis

was performed in January 2000. The last follow-up time for the purposes of the analysis was fixed as October 1999.

Patients' characteristics are presented in Table 1. A total of 170 patients were included in the study, 84 patients were randomised into arm A (cytarabine–5-FU–cisplatin) and 86 patients into arm B (5-FU–cisplatin) (Fig. 1). 10 patients from arm A were considered not to be evaluable for activity in the final analysis: 5 patients were excluded following randomisation because they did not meet the inclusion criteria, mostly because their nodal status was lower than the one needed for this study; they were treated as appropriate, but were excluded because they did not belong to the 'poor prognostic group' as defined for this study; 2 patients had a protocol violation, and 3 patients refused treatment after recovery from the toxicities of the first cycle. 6 patients from arm B were considered not to be evaluable for activity, 2 of them because they did not meet the inclusion criteria, 1 of them because he developed delirium tremens in the intercycle interval (unrecognised chronic aethylism), and 3 of them because they refused further treatment following recovery from the toxicities experienced after the first cycle. Non-evaluable patients were, however, included in the survival analysis. The randomised non-eligible patients were included in the intent-to-treat response analysis but, whatever their response, were not considered as responders. So, for the intent-to-treat analysis of the response rate, the total number of patients was 170 and for the analysis based on the evaluable patients the total number was 154. For the survival analysis, non-eligible patients (i.e. those with a low nodal status) were excluded, making 79 patients evaluable for survival from arm A and 84 from arm B (a total of 163 patients). Both groups were well balanced according to all of the entry data, both in the intent-to-treat patient groups as well as in the available patient groups.

Table 1
Patients' characteristics

Characteristic	Arm A ($n=84$)	Arm B ($n=86$)
Evaluable for activity	74	80
Evaluable for toxicity	84	86
Sex		
Male	81	79
Female	3	7
Age (years)		
Median (range)	52 (25–73)	54 (40–72)
Performance status		
0 + 1	42	43
2 + 3	42	43
Disease extent		
Locoregional	66	63
Metastatic[a]	18	23
Primary tumour (PT)		
Present	61	57
Local relapse[b]	6	9
Absent	19	20
Nodal disease		
Present	84	85
Absent	0	1
Localisation of primary tumour[c]		
Mesopharynx	28	29
Hypopharynx/larynx	46	44
Nasopharynx	5	5
Other	5	8
Previous treatment		
Irradiated	22	23
Not irradiated	62	63
Candidates for additional treatment modalities[d]	32	43

All data are related to all enrolled patients whether evaluable or not.

[a] Metastatic sites in arm A included lungs in 17 patients, liver in 1, soft tissue in 1, pleura in 2; metastatic sites in arm B included lungs in 20 patients, liver in 2, soft tissue in 1, mediastinum in 3; several patients from both arms had more than one distant metastatic site.

[b] Patients that had previous supposedly radical surgery.

[c] Localisation of the primary tumour, irrespective whether the tumour was present or not at the moment of inclusion into the study.

[d] As described in the Material and methods section; non-eligible patients (low nodal volume) are not included in these numbers.

The mean dose intensities of cisplatin and 5-FU were nearly identical in both arms (96 and 96% for cisplatin, 94 and 96% for 5-FU). The dose intensity of cytarabine in arm A was 93%.

The overall treatment results in terms of response categories and RR of the evaluable patients are presented on Table 2. The overall RR in arm A was 48/74 (65%) and 36/80 (45%) in arm B, thus it was significantly higher in arm A ($P=0.013$). There was only a slight overlapping of the 95% CIs. The power for $P=0.05$ was 80% one-sided and 70% two-sided.

On an intent-to-treat basis, the overall RR was 57% in arm A and 42% in arm B, with a larger overlapping of the CIs (47–67% versus 32–52%). The difference was still statistically significant ($P=0.046$), but the power for $P=0.05$ was lower compared with the difference in the evaluable patient analysis (64% one-sided, 51% two-sided).

The percentage of patients who achieved a clinical response making complementary radiotherapy, preceded or not by surgery, feasible was significantly higher in arm A. In arm A, the proportion of such patients was 26/32 versus 16/43 in arm B ($X^2=14.44$, $P=0.00015$; for $P=0.01$ power is 85%).

There was a significant difference in survival between the two arms in favour of arm A ($P=0.009$). The overall survival of patients from the two arms is shown in Fig. 2. The median survival in arm A was 13 months and 8 months in arm B. The probability of 1-year survival was 0.58 for patients in arm A and 0.28 for patients in arm B. The difference in survival was lost after the 18th month. The probability of survival at 2 years was 0.14 for patients in arm A and 0.10 for

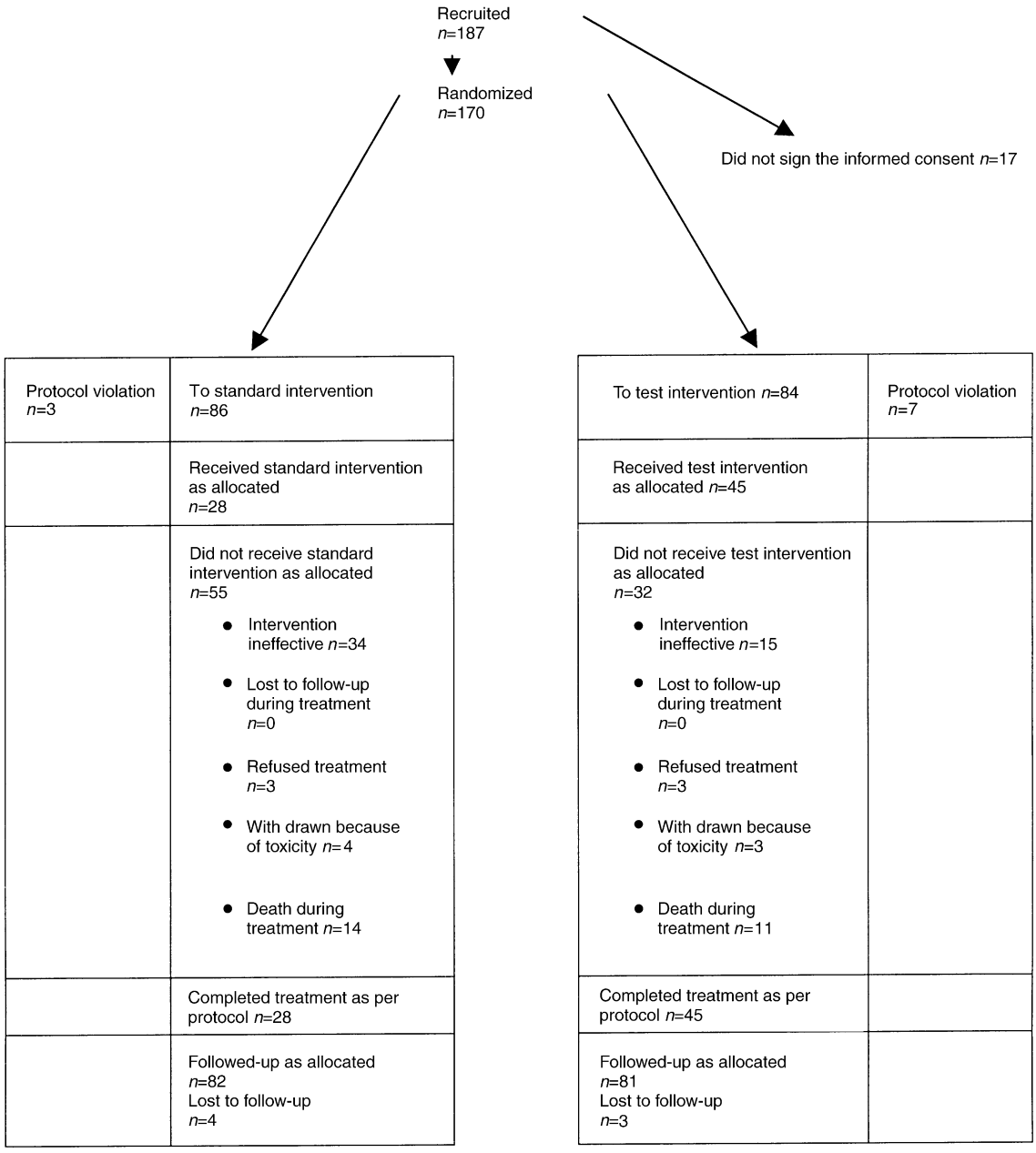

Fig. 1. Flow chart of patients in the trial.

patients in arm B, and at 3 years 0.08 and 0.04, respectively.

The difference in survival was mainly due to a significantly better survival of patients with advanced locoregional disease who had not received any previous irradiation treatment (Fig. 3). The median survival of patients in this subgroup was 13 months in arm A and 8 months in arm B. The probabilities of survival at 12 months were 0.61 for arm A and 0.33 for arm B; at 24 months, they were 0.21 and 0.08, respectively, again in favour of patients in arm A.

The overall survival of the patients who experienced a relapse of disease within a previous irradiation field was not significantly different, although the probability of survival at 12 months was 0.44 for patients in arm A and 0.19 for patients in arm B; median survivals were 11 and 8 months, respectively. The overall survival of the patients presenting with a metastatic disease was not different in the two arms, although there was a survival benefit in favour of arm A between the 7th and 13th months; the 1-year survival probabilities were 0.55 for patients in arm A and 0.21 for patients in arm B. However, it is worth noting that the number of patients in these two subgroups was rather small.

The response rates in patients within different performance status categories were compared between the two arms. In arm A, there were 40 patients with performance status 0+1 evaluable for response and 42

Table 2
Response to treatment of evaluable patients

Response category	Arm A ($n=74$)	Arm B ($n=80$)
Complete response	8/74 (11%)	7/80 (9%)
Partial response	40/74 (54%)	29/80 (36%)
Stable disease	11/74 (15%)	10/80 (12.5%)
Progressive disease	15/74 (20%)	34/80 (42.5%)
Overall response rate (RR)	48/74 (65%)	36/80 (45%)
95% confidence interval for RR	53–75%	35–56%

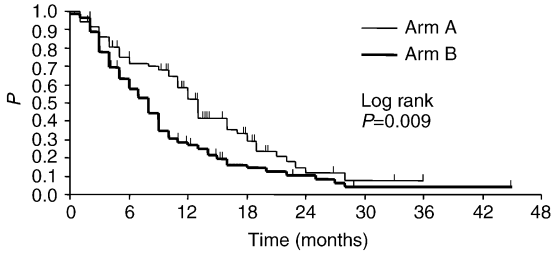

Fig. 2. Overall survival. *P*, probability.

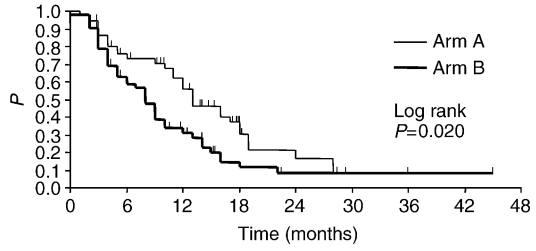

Fig. 3. Overall survival for patients with loco-regionally advanced disease who had not received any previous treatment.

patients in arm B. The response rate of the evaluable patients for this performance status category was 24/40 (60%, 95% CI 45–75%) in arm A and 25/42 (60%, 95% CI 44–75%) in arm B. Thus, there was no difference in the response rates (Pearson Chi-square test, $P=0.965$). For the performance status category 2+3, in arm A there were 34 patients evaluable for response and 38 patients in arm B. The response rate of these patients was 24/34 (71%, 95% CI 55–86%) in arm A and 11/38 (29%, 95% CI 14–44%) in arm B; this difference was highly significant in favour of arm A (Pearson Chi-square test, $P<0.0001$). It could also be of interest to note that in patients achieving a response this response occurred faster in arm A (criteria for response were met in 28/48 patients after the first cycle and 14/48 after the second cycle) than in arm B (criteria for response were met in 5/36 patients after the first cycle and in 13/36 after the second cycle).

In 8 patients from arm A and 3 patients from arm B, chemotherapy was stopped because of progression after an initial stabilisation or response.

Table 3
Toxicity data expressed per number of cycles

Toxicity parameters	Toxicity grade	Arm A[a] ($n=316$)[b]	Arm B[a] ($n=324$)[b]	*P* value
Haemoglobin	III+IV	7	6	N.S
Leucocytes	IV	53	14	<0.01
Granulocytes	IV	50	14	<0.01
Platelets	III+IV	73	12	<0.01
Haemorrhage	Any	9	2	0.039
Stomatitis	Any (I–IV)	9	12	N.S
Nausea/Vomiting	Any (I–IV)	95	79	N.S
BUN/creatinine	Any (I–IV)	7	14	N.S
Infection	Any (I–IV)	15	7	N.S
Cardiac rhythm/function	Any (I–IV)	18	17	N.S
Diarrhoea	Any (I–IV)	7	5	N.S

BUN, blood urea nitrogen; N.S., non significant.
[a] Number of recorded cycles presenting the mentioned toxicity grade.
[b] Total number of cycles given between parentheses.

A summary of toxicities per number of cycles given in the two arms, is presented in Table 3. No other toxicities except those presented in this table were recorded during the study, except for a small amount of alopecia. Regimen A, incorporating cytarabine was significantly more toxic haematologically, more so for platelets than for granulocytes. The median nadir of granulocytopenia occurred on day 10 in arm A and on day 15 in arm B. Febrile neutropenia also occurred more frequently in arm A, but this was of borderline significance ($P=0.0726$). Haemorrhage, when present, occurred only in form of slight petechial rash on the legs. Nausea/vomiting seldom exceeded grade II. In 7 patients (3 from arm A and 4 from arm B), the treatment was stopped because of cardiotoxicity. In general, the excess of toxicities in arm A was manageable, although some cases of troublesome haematological toxicity did occur. A summary of the toxicities per patient is given in Table 4, and a summary of the toxicities in cycles 1, 2, 4 and 6 in Table 5.

11 patients from arm A and 14 patients from arm B were identified who died during the first month following any chemotherapy cycle (Table 6). Four deaths in arm A were caused by febrile neutropenia and two deaths in arm B were attributed to 5-FU cardiotoxicity. One patient from each arm died from suffocation caused by food boluses (both patients has an extensive, i.e. T4 carcinoma of the hypopharynx and achieved an excellent near CR of their primary tumour). Because haematological toxicity of the regimen was identified early in the course of the study, patients from arm A appear to be better monitored as only one case of death from arm A remained unresolved. On the contrary, the exact cause of death in 4 patients from arm B remained undocumented, although the heteroanamnestic data suggested a late appearing febrile neutropenia.

Table 4
Summary of maximal toxicities registered per patient

	Arm A ($n=84$)					Arm B ($n=86$)				
Toxicity grade	0	1	2	3	4	0	1	2	3	4
Toxicity parameter										
Haemoglobin	54	12	13	4	1	68	9	5	4	0
Leucocytes	35	6	11	9	23	61	11	5	4	5
Granulocytes	46	2	7	5	24	70	6	2	4	4
Platelets	32	6	6	14	26	72	4	3	4	3
Haemorrhage	75	3	4	2	0	85	1	0	0	0
Stomatitis	77	3	2	1	1	77	4	2	3	0
Nausea/vomiting	42	10	28	4	0	48	9	27	2	0
Diarrhoea	75	6	3	0	0	81	1	3	1	0
BUN/creatinine	77	6	1	0	0	76	10	0	0	0
Infection	71	2	6	1	4	80	0	1	3	2
Cardiac	71	5	1	5	2	68	6	10	1	2

BUN, blood urea nitrogen.

Table 5
Summary of toxicities per chemotherapy cycle

		Arm A				Arm B			
Cycle no.		1	2	4	6	1	2	4	6
Number of patients		84	70	50	18	86	79	44	19
Toxicity parameter/grade									
Haemoglobin	III	1	1	2	0	3	1	0	1
	IV	0	0	0	0	0	0	0	0
Leucocytes	III	9	9	1	0	3	3	0	1
	IV	21	11	0	0	3	2	0	0
Granulocytes	III	5	5	0	0	4	2	0	1
	IV	22	10	0	0	2	3	0	0
Platelets	III	14	7	2	0	4	1	1	0
	IV	20	8	0	0	2	1	0	0
Haemorrhage	Any	3	2	1	0	0	0	1	0
Stomatitis	I+II	5	1	1	0	4	2	0	0
	III+IV	2	0	0	0	2	2	0	0
Nausea/vomiting	I+II	28	23	16	5	22	19	13	4
	I+IV	2	0	1	0	2	0	0	0
BUN/creatinine	I+II	6	0	1	0	5	3	1	0
	III+IV	0	0	0	0	0	0	0	0
Infection	Any	12	1	1	0	2	1	1	0
Cardiac	Any	5	3	4	1	6	6	1	0

BUN, blood urea nitrogen.

4. Discussion

For over 25 years, different combination treatments and single drug schedules have been investigated in advanced head and neck malignancies. As early as 1975, it appeared evident that combination chemotherapy achieved a higher response rate than single agents; a number of drugs have been identified as devoid of significant antitumour activity in tumours of head and neck areas. Cytarabine was one of those inactive agents [24]. As cytarabine is ineffective in head and neck cancer, it is our opinion that the studies combining cisplatin and cytarabine should not be considered as combination chemotherapy studies in the strict sense of the term, but as studies with a single cytotoxic drug, i.e. cisplatin, with its anti-tumour activity being modulated by cytarabine. It is also our opinion that this study does not compare a two-drug combination to a three-drug combination, but should be considered as a study of a standard regimen for head and neck cancer, i.e. cisplatin plus 5-FU, the latter being applied as a 4-h infusion [21] compared with the same standard regimen but with the cisplatin antitumour activity modulated by high-dose short infusional cytarabine.

Table 6
Deaths within 1 month of the last chemotherapy application

Cause	Arm A	Arm B
Tumour/chemotherapy-unrelated	1	1
Tumour progression	3	5
Chemotherapy-related		
Total	5	3
Febrile neutropenia	4	1
Cardiac	0	2
Steven–Johnson syndrome	1	0
'Wrong swallowing'	1	1
Unknown	1	4
Total	11	14

In early *in vitro* studies of synergy between cytotoxic drugs, the efficacy of cisplatin plus 5-FU was compared with cisplatin plus cytarabine on head and neck carcinoma cells in a monolayer and in multicellular tumour spheroid systems [25]. Both combinations showed a synergistic interaction but the cisplatin plus cytarabine combination was always the more synergistic [25]. 5-FU is an active drug *per se* in head and neck cancer, while cytarabine is not. Thus, the synergy of cisplatin plus 5-FU involved both modulation and additive cytotoxic activity; the synergy of cisplatin and cytarabine involved only a modulating action of cytarabine on the cytotoxic activity of cisplatin, cytarabine did not act as a cytotoxic drug in the strict sense of the term. The rationale for our study was to potentiate the cytotoxic activity of cisplatin with cytarabine in the cisplatin plus 5-FU combination and to ascertain whether such a 'potentiated' regimen would prove superior to the 'non-potentiated' one.

As already stated, the clinical data concerning the cytarabine-related enhancement of cisplatin cytotoxicity ranged from overtly negative [26] to promising [14]. Our previous study, which demonstrated the possibility of reversal of the resistance to cisplatin in at least some patients with advanced head and neck cancer comes into the category of 'promising' clinical data [19]. However, a literature search for related data found no randomised studies of cisplatin alone versus cisplatin plus

cytarabine or cisplatin in combination regimens versus cisplatin plus cytarabine as part of combination regimens.

So, the present study is the only study investigating cytarabine/cisplatin synergy in a poor prognostic population with enough patients for sufficient power, and the only randomised study comparing the cytarabine-potentiation of a standard regimen.

The choice of patients in previous studies will certainly have affected the results, both in terms of RR and survival. However, phase II studies are mutually non-comparable and clinical aspects of the synergism between the two drugs might have been missed due to the lack of a randomised comparison. Expected toxicities might prevent investigators from performing such a study and this affected the choice of patients in our study; the selected group was known to do poorly in the palliative, neoadjuvant or the aggressive chemo-radiotherapy settings [27]. A significant percentage of our patients would probably have been fit for best supportive care only; approximately half of them would not be eligible for classical new drug or drug combination phase II studies because of their low performance status. The choice of patients is probably related to the relatively low overall RR observed to the cisplatin-5-FU regimen: however, the RR in the subgroup of patients with performance status 0 and 1 appeared comparable to the response usually achieved in other studies of this combination. Nevertheless, PR in these patients was not synonymous with a downstaging that enabled the application of further treatment modalities.

Indeed, the RR that is achieved in very advanced head and neck cancer cases is probably not the pivotal parameter determining overall survival; in head and neck cancer patients, and CRs in very advanced cases are rather infrequent. That is why we have added a second parameter, i.e. the proportion of patients who achieved a clinical response making other treatment modalities feasible.

Arm A of our study appeared superior both in terms of overall RR and downstaging in the subset of patients with advanced loco-regional disease without previous irradiation treatment. Improved survival in this arm could result from the difference in the percentage of patients who achieved downstaging and who were shifted to other treatment modalities. Unfortunately, the survival benefit was no longer evident after 2 years. Interestingly, the difference in the RRs between the two arms was mainly due to differences among the responders entering the study, in particular those with a low performance status. These patients fared better in the cytarabine arm, a fact that might be related to the observation that the response in responders was achieved faster in the cytarabine arm, possibly helping these patients to recover their performance status faster. Other categories of patients, apart from those with advanced loco-regional disease with no previous irradiation treatment, also appeared to benefit from the addition of cytarabine to cisplatin and 5-FU, as evidenced by Z-values at particular periods during the follow-up; the lack of a difference in overall survival might be the result of the lack of power of this small sample. However, subgroup analyses are often misleading, as they are not statistically powered enough to provide definite statements. Caution is therefore needed in the interpretation of subgroup outcome data.

The addition of cytarabine certainly resulted in more haematological toxicity, but the other toxicities appeared similar. Later cycles were better tolerated than the first one; However, the interpretation of these data is slightly confusing (the selection of patients for further chemotherapy or better tolerance is related to the tumour response) and requires caution. Haematological toxicity was manageable, although troublesome at times. It required daily monitoring of the peripheral blood count at least until day 10, i.e. the most frequent day of the granulocyte nadir value. The exact haematological toxicity in arm B might have been underestimated as it appeared to be mostly 5-FU-related, and occurred late.

The treatment of advanced head and neck cancer is still a problem that is far from solved. Combined modality treatments include induction chemotherapy prior to loco-regional treatment (surgery or radiotherapy) with or without additional chemotherapy afterwards [28] and concomitant chemo-radiotherapy [29–31]. Among the new drugs, both docetaxel and paclitaxel appeared to be active [32,33]. However, at the moment, the standard regimen is still the cisplatin plus 5-FU combination. Paclitaxel has been added to the combination at a dosage of 135 mg/m^2 per cycle with a response rate of 60%; 7/25 patients had grade IV mucositis and neutropenia was a major toxicity [34]. Addition of docetaxel to the same combination resulted in a response rate of 44%, but most of the patients received granulocyte-colony stimulating factor between days 4 and 8; 15% of courses were complicated by febrile neutropenia [35].

In order to improve the efficacy of the cisplatin plus 5-FU combination, our study was based on a different approach. Instead of adding a third cytotoxic drug in the strict sense of the term, we tried to achieve a better efficacy by potentiating the cytotoxic effect of cisplatin. Whether cytarabine (an inactive drug *per se* in head and neck cancer) is the ideal drug to achieve this goal, remains a subject for debate, mainly because of the additional haematological toxicity. In future studies, we intend to try to overcome this by reducing the cytarabine dosage to 500 mg/m^2 within the same schedule of administration. The next step could be to use this combination as a neoadjuvant in better prognostic cases, preceding chemo-radiotherapy treatment that according

to recent data from the controlled clinical trials seems to be superior to standard radiotherapy. Our study indicates that enhancement of the cytotoxicity of the cisplatin by the addition of short infusional high-dose cytarabine to the cisplatin plus 5-FU regimen did induce both a response and survival benefit, but resulted in additional clinically significant haematological toxicities. Nevertheless, modulation of cisplatin cytotoxicity in order to enhance the activity of the drug in head and neck cancer could be of interest for further study.

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