Phase II Trial of Chemotherapy with 5-Fluorouracil, Bleomycin, Epirubicin, and Cisplatin for Patients with Locally Advanced, Metastatic, or Recurrent Undifferentiated Carcinoma of the Nasopharyngeal Type

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BACKGROUND. The aim of this study was to evaluate the toxicity and efficacy of the combination of 5-fluorouracil, bleomycin, epirubicin, and cisplatin (FBEC) in the treatment of patients with undifferentiated carcinoma of nasopharyngeal type (UCNT). The study included patients with metastatic or recurrent disease (Group A) and previously untreated patients with locally advanced nonmetastatic disease ($T \geq 3$ or any T, $N \geq 2$, M0, according to 1987 criteria of the International Union Against Cancer and the American Joint Committee on Cancer (Group B).

METHODS. From January 1992 to November 1996, 49 patients with histologically proven UCNT were treated with intravenous (i.v.) 5-fluorouracil (700 mg/m^2/day by continuous infusion for 4 days), epirubicin (70 mg/m^2 i.v. on Day 1), Bleomycin (10 mg i.v. bolus on Day 1 followed by 12 mg/m^2/day by continuous infusion for 4 days), and cisplatin (100 mg/m^2 on Day 5); this regimen was repeated every 21 days. Six cycles were given to Group A (26 patients), with bleomycin omitted during the last 3 cycles. In Group B (23 patients), only 3 cycles were given, followed by conventional radiotherapy (70 gray for 7 weeks).

RESULTS. Of the 26 patients entered in Group A, 23 were evaluable for response. Nine complete responses (CRs) and 9 partial responses (PRs) were assessed, for a 78% objective response rate (ORR) (95% CI: 56–92). Three patients are alive with no evidence of disease after 43, 61, and 73 months, respectively. These patients achieved a CR with chemotherapy followed by consolidating radiotherapy to their target lesions. In Group B, the ORR was 91.5%, with 5 CRs (22%) and 16 PRs (69.5%) assessed in the 23 patients. Three months after the end of radiotherapy, the ORR was 87% (20 patients). After a median follow-up of 51 months (range, 24–67months), 15 patients (65%) are alive without evidence of disease. Forty percent of cycles (51% in Group A, 25% in Group B) resulted in Grade 4 neutropenia, with fever and/or sepsis in 9.5%. Mucositis was seen in 42% of pretreated patients. There were 3 treatment-related deaths (2 from complications of infection and 1 bleomycin fibrosis at a total dose of 160mg/m^2), all of them in Group A.

CONCLUSIONS. The FBEC regimen has good activity, with durable responses in patients with locally advanced, metastatic, or recurrent UCNT. This regimen is safe for patients with locally advanced disease, but close follow-up and supportive measures are needed when it is used to treat those with metastatic or recurrent disease. ***Cancer*** **1999;86:1101–8.** © *1999 American Cancer Society.*

KEYWORDS: nasopharyngeal carcinoma, neoadjuvant chemotherapy, palliative chemotherapy, combination chemotherapy.

TABLE 1
Chemotherapy Protocols for Patients with Undifferentiated Carcinoma of the Nasopharyngeal Type at the Institute Gustave Roussy

Chemotherapy	PBF (1985–1987)	BEC (1987–1990)	FMEP (1990–1991)	FBEC[a]
Cisplatin	100 mg/m^2, Day 1	100 mg/m^2, Day 1	100 mg/m^2, Day 1	100 mg/m^2, Day 5
Bleomycin	15 mg, i.v. push, then 16 mg/m^2/day × 5 days c.i.v.	15 mg, i.v. push, then 16 mg/m^2/day × 5 days c.i.v.	—	10 mg, i.v. push, then 12 mg/m^2/day × 4 days c.i.v.
5-Fluorouracil	650 mg/m^2/day × 5 days c.i.v.	—	800 mg/m^2/day × 4 days c.i.v.	700 mg/m^2/day × 4 days c.i.v.
Mitomycin	—	—	10 mg/m^2, Day 1, i.v. every other cycle	—
Epidoxorubicin	—	80 mg/m^2/Day 1	70 mg/m^2/Day 1	70 mg/m^2/Day 1
Cycles every week	4	3	3	3

PBF: cisplatin, bleomycin, and 5-fluorouracil; BEC: bleomycin, epirubicin, and cisplatin; FMEP: 5-fluorouracil, mitomycin, epirubicin, and cisplatin; FBEC: 5-fluorouracil, bleomycin, epirubicin, and cisplatin; IV: intravenous; c.i.v.: continuous i.v. infusion.
[a] Current study.

Undifferentiated carcinoma of nasopharyngeal type (UCNT) is a particular head and neck epidermoid lineage tumor that is related to the Epstein–Barr virus (EBV), with sociocultural, geographic, and ethnic-selective endemic features. The incidence of UCNT is high in Southeast Asia and the Mediterranean basin, whereas, in Japan, Europe, and America, it is a rare malignancy.[1,2] The often rapid growth and highly metastatic behavior of this cancer accounts for the high rate of treatment failure despite its marked radiosensitivity and high rate of local control.[3]

The use of chemotherapy in metastatic UCNT patients results in a high percentage of objective responses, many of long duration. Our three previous Phase II protocols in the metastatic and neoadjuvant setting, based on drugs considered to be active in carcinomas of epidermoid origin,[4] have been progressively incremental in their conception and design.

In light of the accumulated efficacy and tolerance experience, and with the aim of improving the overall response rate (ORR) and patient survival, a new Phase I–II study of a 4-drug combination with 5-fluorouracil (5-FU), bleomycin, epirubicin, and cisplatin (FBEC) was started in January 1992 (Table 1). Cisplatin was administered on the last of the 5-day schedule in an attempt to avoid any eventual decrease in renal bleomycin clearance secondary to cisplatin-induced renal injury. The toxicity and activity results of this new regimen in the treatment of 49 patients with UCNT (23 patients with locally advanced disease and 26 patients with recurrent or metastatic disease) are presented.

MATERIALS AND METHODS

Between January 1992 and November 1996, 49 patients with histologically and serologically proven UCNT were treated with FBEC combination chemotherapy. Table 1 summarizes the doses and schedules of the present combination as well as our previous combination protocols used for patients with this disease.[5–7]

Twenty-six patients with metastatic recurrent UCNT were treated with chemotherapy alone (Group A), and 23 patients with previously untreated, locally advanced nonmetastatic disease ($T \geq 3$ or any T with $N \geq 2$) received three cycles of combination chemotherapy followed by locoregional radiation therapy (Group B). All patients underwent a pretherapeutic work-up, including clinical history and examination, biopsy, head and neck computed topography (CT) scan, chest X-ray, abdominal ultrasound, bone scan, a complete blood count, erythrocyte sedimentation rate determination, 24-hour urine creatinine clearance, routine chemistries, and EBV serology (immunoglobulin G [IgG] viral capsid antigen [VCA], IgG early antigen [EA], IgA VCA, IgA EA). Functional respiratory tests, which were part of the baseline work-up, were repeated after the second cycle of chemotherapy or when the total dose of dose bleomycin given exceeded 300 mg/m^2. Abdominal and thoracic CT scans were performed when any doubts were raised by routine examinations, abnormal biochemical tests, or suspect symptoms. Patients were staged according to the American Joint Committee on Cancer–International Union Against Cancer (AJCC-UICC) 1987 TNM classification.[8]

Therapeutic Schedules

Chemotherapy

In patients with metastatic or recurrent disease (Group A), chemotherapy consisted of 6 cycles of 5-FU

(700 mg/m^2/day continuous infusion on Days 1–4); epirubicin (70 mg/m^2 intravenously [i.v.] on Day 1); bleomycin (10 mg i.v. bolus on Day 1 followed by 12 mg/m^2 on Days 1–4 by continuous infusion); and cisplatin (100 mg/m^2 i.v. on Day 5) repeated every 3 weeks. Bleomycin was omitted in the last 3 cycles. Unlike in our previous therapeutic combination schedules,[5–7] cisplatin was given on Day 5 in an attempt to decrease the likelihood of bleomycin lung toxicity (observed during our previous experience, in which cisplatin was given on Day 1 of the combination).

In patients with locally advanced nonmetastatic disease (Group B), 3 cycles of the same protocol were delivered before reassessment and locoregional radiotherapy. Standard hydration (4–6 L of half-normal saline, 5% over 24 hours) with mannitol-induced diuresis and an anti-HT_3 antiemetic-based regimen were given with the cisplatin administration. Adequate renal (creatinine < 120 μmol/L), hematologic (absolute neutrophil count $> 1.5 \times 10^9$/L, platelets $> 100 \times 10^9$/L), and liver function tests (alanine aminotransferase and aspartate aminotransferase ≤ 2.5 N) were required before each cycle.

Locoregional radiotherapy

Locoregional radiotherapy was started 2–3 weeks after cycle 3 of chemotherapy. Radiation therapy was delivered with cobalt-60 or a 4 MeV linear sources accelerator at a dose of 2 gray (Gy)/fraction, with 5 daily fractions per week. The total dose planned was 70 Gy over 7 weeks to the nasopharyngeal tumor and its extensions, as defined by pretherapeutic CT scan; 65 Gy/6.5 weeks to the initially involved lymph node areas; and 50 Gy/5 weeks to the rest of the neck. The radiotherapy technique has been described previously.[9] Locoregional disease response to treatment was evaluated by the same team and imaging techniques 2 weeks after cycle 3 of chemotherapy and was repeated 3 months after the end of radiation therapy.

A systematic follow-up with locoregional examination and metastatic work-up was done every 6 months for 18 months and once a year thereafter. In patients with metastatic or recurrent disease, the evaluation of treatment response was performed 3 weeks after cycles 2 and 6 of chemotherapy and every 3 months thereafter.

The World Health Organization (WHO) standard criteria were used for toxicity and response evaluation. Patients who received at least 1 cycle were considered evaluable for toxicity; those who withdrew after only 1 cycle for any reason other than disease progression were considered not evaluable for response assessment.

TABLE 2
Patient Characteristics

Characteristic	Value
Gender (M/F)	37/12
Age in yrs (range)	46 (15–69)
PS (WHO)	
0	35
1	10
2	4
Metastatic or recurrent disease	26
Previously untreated	3
Previously treated	23
RT alone	9
CT alone	1
CT + RT	13
Site of disease	
Locoregional recurrence alone	13
Metastatic ± locoregional disease	13
Bone	6
Liver	4
Lung	2
Extraregional lymph nodes	4
No. of metastatic sites	
1	10
≥2	3
Locoregional (M0) disease	23
T1/T2	1/6
T3/T4	5/11
≤N2b	5
N2c	14
N3	4

M: male; F: female; PS: performance status; WHO: World Health Organization; RT: radiation therapy; CT: chemotherapy.

Patient characteristics

Patient characteristics are summarized in Table 2. Twenty-three patients had locally advanced nonmetastatic disease (Group B), and 26 patients were confirmed to have recurrent or metastatic disease (Group A). Follow-up data were obtained through October 1998.

The TNM distribution in Group B shows that 48% of patients had base of skull and/or cranial nerve involvement (T4), and 78% of patients had bilateral lymph nodes $>$ 3cm (N2c) or unilateral or bilateral lymph nodes $>$ 6 cm (N3). Among the patients in Group A, 13 patients (50%) had locoregional recurrence only, 5 patients (19%) had metastatic disease only, and 8 patients (31%) had both locoregional recurrence and distant metastases. Pretreatment consisted of chemotherapy and radiotherapy in 13 patients, chemotherapy alone in 1 patient, and radiotherapy alone in 9 patients.

TABLE 3
World Health Organization Classification Grade 3–4 Toxicities

Toxicity	Group A, metastatic/recurrent	Group B, local/untreated
Evaluable patients	26	23
Evaluable/given cycles	98/100	67/67
Hematologic toxicity (patients/cycle)		
Leucopenia		
Grade 3	18/31	6/7
Grade 4	11/17	6/9
Neutropenia		
Grade 3	15/26	6/7
Grade 4	12/24	7/10
Thrombocytopenia		
Grade 2	9/18	5/6
Grade 3	9/10	4/5
Grade 4	2/3	1/1
Mucositis		
Grade 3	9/16	2/5
Grade 4	2/2	0
Febrile neutropenia	9/11	3/5
Toxic death	3	0

RESULTS

Toxicity

Chemotherapy-induced toxicity is presented separately according to the frequency observed in both patient groups (Table 3).

Group A

In Group A, 98 out of 100 given cycles and all 26 patients were evaluable for toxicity. A median of 4 cycles/patient was given (range, 1–6 cycles/patient). Grade 3–4 neutropenia, which was frequent, was observed in 50 cycles (51%) and in 22 patients (84.5%). The mean duration of neutropenia was brief, with a median of 3 days (range, 1–7 days). Febrile neutropenia episodes occurred in 11 cycles (11%) and in 9 patients (34.5%). Grade 3–4 thrombocytopenia was observed in 13 cycles (13%) and in 9 patients (34.5%). Grade 3 anemia was noted in 9 cycles. Six patients (23%) required red blood cell transfusions. Grade 3–4 mucositis was seen in 18 cycles and in 11 patients: All of them had undergone previous locoregional irradiation. Other toxicities noted were reversible alopecia (Grade 3) in all treated patients, pulmonary complications (subclinical radiological changes; Grade 2) in 3 patients, 5-FU-related transient cardiomyopathy in 1 patient; and significant clinical ototoxicity in 2 patients. There were 3 treatment-related deaths among the 26 patients. One of these deaths was related to neutropenic sepsis after cycle 2 of chemotherapy. The second patient died of listeriosis pneumonia after cycle 2. The third patient died of bleomycin-related pulmonary complications after cycle 4, which did not include bleomycin. This patient, age 58 years, received a total dose of 160 mg/m^2 of Bleomycin and had normal renal function. It is noteworthy that the patient's brother, who also had an UCNT, had died 3 years earlier from a lethal bleomycin-related lung fibrosis after a total dose of 225 mg/m^2.

Group B

In Group B, all the 67 cycles given and all 23 patients were evaluable for toxicity. Severe toxicities were less frequent than in Group A. Grade 3–4 neutropenia was observed in 17 cycles (25%) and in 13 patients (56.5%). Five episodes of febrile neutropenia were seen in 3 patients with no complications. Grade 3–4 thrombocytopenia was rare, seen in only 6 cycles (9%) and 4 patients (17%). Grade 3 mucositis was observed in 5 cycles (7.5%) and in 2 patients. There were no treatment-related deaths. Radiation therapy generally was well tolerated, with no increase in acute (except for severe mucositis-related, reversible, weight loss for all patients at the end of radiotherapy) or late toxicities.

Treatment Results

Group A

Of the 26 patients entered, 23 were evaluable for response. Two patients refused treatment after cycle 1, and one patient died of treatment-related toxicity (described above; neutropenic sepsis after 2 cycles). Eighteen patients achieved an objective response (9 CRs and 9 PRs) for an ORR of 78% (95% confidence interval [CI], 56–92) in evaluable patients. The intent to treat ORR was 69% (95% CI, 48–86). We also observed 4 patients with disease progression and 1 patient with a long stabilization (11 months). This patient achieved a minor response after 4 cycles of FBEC in a locoregional relapse and thereafter continued treatment with weekly vinorelbine until progression. The overall median response duration was 9 months (3+–70+ months). The median response durations for CRs and PRs were 11 months (3+–70+ months) and 8.5 months (3.5–17.5 months), respectively.

After a median follow-up of 58 months (range, 20–81 months), 4 patients were alive, and 2 patients were lost to follow-up 2 months and 5 months after the start of study treatment, respectively. The median duration of survival for all patients in the recurrent/metastatic cohort was 15 months (range, 2–73+ months), with a median time to progression of 9 months (range, 1–73+ months) (Fig. 1). As of October 1998, three patients were alive in first remission with no evidence of disease (clinical or radiological) at 43+, 61+, and 73+ months. The first two patients had exclusive locoregional recurrence, and the third pa-

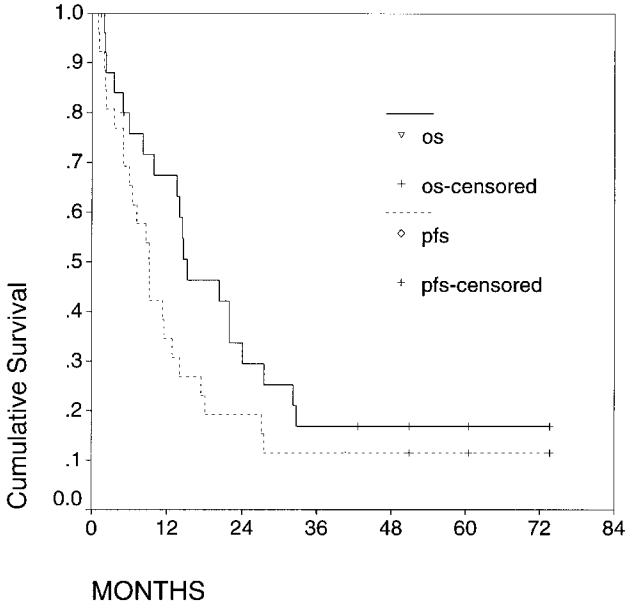

FIGURE 1. Overall survival (os) and progression free survival (pfs) for patients with metastatic or recurrent carcinoma of the nasopharynx.

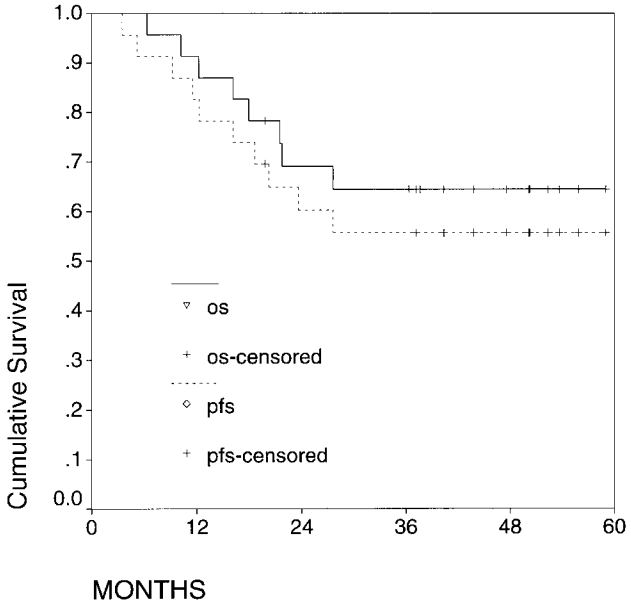

FIGURE 2. Overall survival (os) and progression free survival (pfs) for patients with locally advanced carcinoma of the nasopharynx.

tient had metastatic disease (lung and mediastinal lymph nodes). All 3 of these patients received consolidating radiotherapy (50 Gy) to their target sites after achieving a CR with chemotherapy.

Objectives responses were seen in all metastatic sites. CRs were assessed in liver (3 of 4 patients), lung (1 of 2 patients), and extraregional lymph nodes (2 of 4 patients). PRs were observed in lung (1 of 2 patients), extraregional lymph nodes (2 of 4 patients), and bone (4 of 6 patients). Two of the 4 patients with PRs on bone disease received radiotherapy on bone lesions, because they achieved CRs in the other metastatic sites. In 21 patients who had locoregional recurrences, 7 CRs and 5 PRs were seen, all of them in previously irradiated territory.

Group B

All 23 entered patients were evaluable for chemotherapy response after neoadjuvant chemotherapy. Five patients (22%) experienced a CR, and 16 patients (69.5%) achieved a major PR (>80% disease volume reduction). Two patients had a minor response (>25% and < 50%). The ORR was 91.5% (95% CI, 72–99). All of the patients received the full planned dose of radiotherapy as scheduled, and all but one patient were assessed 3 months after the end of radiotherapy. This patient developed liver and lung metastasis at the end of radiotherapy. Twenty patients achieved a CR to radiation therapy (87%), whereas two patients remained in PR (residual cervical lymph nodes).

As of October 1998, and with a median follow-up of 51 months (range, 24–67 months), 15 patients (65%) were alive with no evidence of disease, all in first remission. Eight patients had died: 6 patients of disease and 2 patients of other causes (1 patient died of septic peritonitis unrelated to treatment while in CR, and 1 patient died after pneumonia 27 months after achieving a PR). The median survival has not yet been reached, and the 4-year overall survival (OS) rate is 58% (Fig. 2).

DISCUSSION

In patients with advanced, nonmetastatic UCNT, the present chemotherapy combination was well tolerated, without serious limiting toxicity. The ORR to the neoadjuvant FBEC combination was high (91.5%), with 22% of CRs to chemotherapy and an 87% local control rate after the full combined-modality treatment. With a median follow-up of 51 months (range, 24–67 months), 65% of patients are still in first remission with no evidence of disease. These results are similar and may compare favorably with the results of our previous Phase II studies[5–7] in terms of efficacy and locoregional control. In the first study, which was conducted between 1985 and 1987, 30 consecutive patients with Stage IV nonmetastatic UCNT received 2 courses of cisplatin, bleomycin, and 5-FU (PBF) followed first by radiotherapy (35 Gy/3–5 weeks) and thereafter by 1 additional course of PBF before the second radiotherapy course (35 Gy/3.5 weeks). An ORR after chemotherapy of 83% was obtained, with 10% of patients achieving a CR. The local control rate

after the end of radiation therapy was 92%. After a median follow-up of 65 months, 14 patients were alive without disease (2 of them after salvage therapy), corresponding to a 47% OS rate. The 4-year disease free survival rate was 35%.[7]

After this experience, between 1987 and 1990, 67 patients with previously untreated, locally advanced, nonmetastatic disease were treated with 3 cycles of a regimen of bleomycin, epirubicin, and cisplatin (BEC) followed by locoregional radiotherapy (70 Gy/7 weeks). The ORR after chemotherapy was 98%; 62% of patients had a CR and 94% of patients achieved local control after completion of chemoradiotherapy. After a median follow-up of 6.5 years, 35 patients were alive with no evidence of disease (2 patients after salvage therapy). The 4-year progression free survival (PFS) and OS rates were 60% and 66%, respectively.[6]

These three consecutive programs show a high ORR to chemotherapy. The rates of CR to chemotherapy were 10% with the first program and were higher with the second program (62%). Locoregional control after radiotherapy treatment was similarly high in all three programs. The eventual added benefit of either anthracycline contribution or the 4-drug versus 3-drug combination from this study against the 3-drug regimen cannot be established clearly without a controlled trial. Furthermore, the variation in dose intensity and dose density between our first protocol (PBF given every 4 weeks) and the subsequent protocols (BEC or FBEC given every 3 weeks) cannot be analyzed reliably due to the large difference in the myelotoxic potentials of the different combination drugs.

To test the value of neoadjuvant chemotherapy, our team started a prospective Phase III trial comparing 3 cycles of the BEC protocol followed by radiotherapy with the same doses of radiotherapy given alone in patients with locally advanced UCNT (N2–3, M0). In total, 339 patients were enrolled in this study. Preliminary results of this trial with a median follow-up of 49 months (range, 23–70 months) showed a significant difference in disease PFS, favoring the chemotherapy arm (32.7% vs, 54.7%; $P < 0.01$).[9] Recently, Al Sarraf et al.[10] reported positive similar results comparing concomitant chemotherapy and radiotherapy with radiotherapy alone in patients with nasopharyngeal carcinoma. A total of 193 patients with Stage III–IV disease were included, and 147 patients were evaluable for survival analysis. A significant difference was observed in both the PFS rate (3-year PFS rate: 15 months vs. 69 months; $P < 0.001$) and the OS rate in favor of the combined arm (3-year survival rate: 47% vs. 78%; $P = 0.005$). It is noteworthy that 59% of the North American patients had WHO Stage I and II histologic types (squamous cell carcinoma). This fact and the lack of a thorough baseline metastatic work-up may account for the poor results of the control arm in the intergroup trial. Nevertheless, the results of these two comparative studies emphasize the effectiveness of chemotherapy added to radiotherapy in the treatment of patients with locally advanced nasopharynx carcinoma.

In patients with metastatic or recurrent UCNT, the FBEC protocol was effective, with an ORR of 78% (39% CRs and 39% PRs). Responses were seen in all metastatic sites, with 75% of CRs in liver metastasis. The median survival was 15 months (range, 2–73+ months), and the median time to progression for the whole cohort was 9 months (range, 1–73+ months). In this pretreated population, the treatment was associated with neutropenia in 50% of cycles, with one-third of patients presenting at least one febrile neutropenia episode. Three patients died of treatment-related toxicity (septic shock, listeriosis pneumonia, and bleomycin pulmonary fibrosis). The patient with fatal bleomycin lung fibrosis was diagnosed after a low dose (160 mg/m^2) in the absence of other associated causes. The fact that the patient's brother had suffered from the same disease and had experienced a similar bleomycin-induced death (at 225 mg/m^2) evokes the possibility of a genetic defect. The gene of bleomycin hydrolase recently has been localized,[12] and its study may be of interest. Forty-two percent of patients experienced severe mucositis, but all of them had received previous locoregional radiation therapy.

Recently, two teams reported similar results in terms of ORR. Siu et al.[11] from the Princess Margaret Hospital treated 69 patients with recurrent or metastatic UCNT with a 5-drug combination (cyclophosphamide, doxorubicin, cisplatin, methotrexate, and bleomycin). They obtained an ORR of 82% (60% intent to treat), with median survival durations of 16 months and 14 months for recurrent locoregional disease and metastatic disease, respectively. The toxicity of this regimen was severe, with 7 treatment-related deaths (8.5%) also reported. Chi et al.[13] from Taiwan reported their experience with a cisplatin, fluorouracil, and leucovorin regimen in 22 patients. The ORR was 68%, with 23% of patients achieving a CR. The median survival was between 14 months and 16 months. This regimen was well tolerated. The median response duration was 20 weeks.

When analyzing these findings and the results of our three previous consecutive trials in metastatic/recurrent UCNT patients (Table 4), it appears that 1) with the PBF protocol,[7] the response rate was high (79% and 19% of CRs in 49 patients), but no objective responses were seen in visceral disease sites, and 3 patients had long term CRs and are alive without

TABLE 4
Characteristics of Patients with Metastatic or Recurrent Undifferentiated Carcinoma of the Nasopharyngeal Type and Results of the Four Protocols

Characteristic	PBF (8)	BEC (7)	FMEP (6)	FBEC[a]
No. of patients entered/assessable	49/44	44/38	46/46	26/23
Age in yrs (range)	36 (16–61)	41 (9–77)	46 (20–72)	46 (15–69)
Gender M/F	36/13	39/5	40/6	22/4
Performance status				
0–1	25	24	35	24
2–3	24	20	11	2
Previously untreated	6	12	4	2
Pretreated	43	32	42	24
RT alone	40	14	22	9
CT ± RT	16	18	20	15
ORR (intent to treat)	38 (79%)	22 (45%)	28 (61%)	18 (69%)
CR	9 (19%)	9 (20%)	4 (9%)	9 (34.5%)
PR	29 (60%)	11 (25%)	24 (52%)	9 (34.5%)
CR by site/no. assessed				
Liver	0/11	2/18	6/17	3/4
Bone	7/37	6/33	7/27	0/6
Bone marrow	0/12	0/8	3/4	—
Lung/pleura	3/12	1/11	1/4	1/2
Extraregional lymph nodes	1/10	3/9	1/5	2/4
Long term NED	3/49	4/44	4/46	3/26

PBF: cisplatin, bleomycin, and 5-fluorouracil; BEC: bleomycin, epirubicin, and cisplatin; FMEP: 5-fluorouracil, mitomycin, epirubicin, and cisplatin; FBE: 5-fluorouracil, bleomycin, epirubicin, and cisplatin; M: male; F: female; RT: radiation therapy; CT: chemotherapy; ORR: objective response rate; CR: complete response; PR: partial response; NED: no evidence of disease.

[a] Current study.

evidence of disease at 181+, 131+, and 135+ months, respectively; and 2) the BEC regimen[6] showed an ORR of 45%, with 20% of CRs in 44 patients (it is noteworthy that CRs were seen in visceral metastatic sites), and 4 patients are still in CR at 90+, 96+, 97+, and 108+ months, respectively. In our first 4-drug combination (5-FU, mitomycin, epirubicin, and cisplatin),[5] 61% of patients achieved an objective response, with 9% of patients achieving CRs, which were seen in all metastatic sites. This protocol had high neutropenia-related morbidity and thrombocytopenia related to mitomycin-C. Four patients were still alive with no evidence of disease at 73+, 76+, 80+, and 95+ months, respectively.

In the current study, there is one long term survivor among the metastatic patients still in CR for over 73 months. This patient had pulmonary and mediastinal metastasis. Although there is a limited number of subjects to establish a statistically valid correlation, there is an increasingly better response rate in visceral disease sites (especially the liver), indirectly supporting an increasing activity of the successive regimens. Since approximately 1993, due to a better knowledge of the disease chemosensitivity and because of care reimbursement changes, geopolitical changes, and immigration policy changes, there has been a significant decline in the number of cases of nasopharyngeal carcinoma seen at the Institut Gustave Roussy that previously were accrued mainly from Southern Italian and North African patient populations. The extended period over which all of these Phase II studies were done makes a formal comparison between different regimens an unfeasible or irrelevant endeavor. Nevertheless, the high level of activity and acceptable toxicity of the 4-drug combination reported here have made it our routine choice for the treatment of patients with locally advanced disease who do not qualify as candidates for prospective controlled trials.

For previously treated relapsing patients or metastatic patients, this regimen is fairly toxic. A platinum-based chemotherapy (a combination of cisplatin and 5-FU with or without leucovorin or cisplatin/anthracycline/bleomycin) remains the standard chemotherapy in this setting, unless the patient's general condition and age motivate a more aggressive approach.

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