*Acta Oncologica 29 (1990) Fasc. 6*

FROM THE CELLULAR CHEMOTHERAPY LABORATORY, IMPERIAL CANCER RESEARCH FUND, AND THE U.K. REPRESENTATIVE OF INTERNATIONAL ADVISORY COUNCIL, NEW YORK CHEMOTHERAPY FOUNDATION, LONDON, ENGLAND.

# THE ROLE OF ADJUVANT CHEMOTHERAPY IN THE TREATMENT OF ADVANCED HEAD AND NECK CANCER

B. T. HILL and L. A. PRICE

**Abstract**

The role of chemotherapy in the multidisciplinary treatment of advanced squamous cell carcinoma of the head and neck remains to be defined. Uncontrolled adjuvant studies integrating chemotherapy with local therapies utilizing a 'sequential' or 'simultaneous' strategy have indicated that high response rates to initial chemotherapy and high complete remission rates are achievable. Both these factors appear to predict for improved survival. Unfortunately results of randomized, controlled studies generally have not confirmed any major overall survival advantage. However, these trials clearly failed to utilize optimal therapies: suboptimal trials yield suboptimal results. Encouraging data from large uncontrolled studies have now provided critical information regarding optimal trial design; a) Since primary tumor site has proved a significant predictive factor for response to treatment and survival, future trials must include sufficient numbers of patients for detailed site-by-site analyses, and b) radical surgery may be omitted without compromising survival by using initial chemotherapy followed by radiotherapy for advanced laryngeal cancer.

*Key words:* Head and neck cancer, adjuvant chemotherapy, initial chemotherapy, laryngeal carcinoma, nasopharyngeal carcinoma, oral cavity tumours, randomized controlled trials.

Adjuvant chemotherapy trials in head and neck cancer, involving the treatment of patients with curative intent, have followed two main approaches. In the first, termed 'sequential' treatment, chemotherapy has been given initially followed by local-regional therapy, whilst the second approach termed 'simultaneous', has utilized either chemotherapy alternating with radiotherapy or the concurrent administration of both modalities.

With the 'sequential' approach many different drugs have been tested as initial treatment, but those most widely used have included cisplatin, 5-fluorouracil and methotrexate, sometimes with the addition of bleomycin or a Vinca alkaloid. The route of drug administration has predominantly been intravenous although intra-arterial chemotherapy has also been evaluated. Generally two or three courses of initial chemotherapy before local treatment, with a range of one to four, have been used. This 'sequential' approach has been widely tested in a number of pilot studies in patients predominantly with stage III or IV disease. The main ones are summarized in Table 1, but unfortunately the small number of patients in many trials has precluded definitive analyses. The only studies involving over 100 patients being those of Price & Hill (12) and of Ervin et al. (9). All these pilot studies, however, have resulted in high overall response rates to initial chemotherapy and in eight of them significant high complete response (CR) rates, ranging from 22% to over 35%, were reported. The survival figures vary, with the poorest being 50% of patients alive at only 11 months and the best figure quoted being 50% survival at 36 months.

In general, the results of these pilot studies were considered encouraging and led to the setting up of a number of randomized, controlled trials testing this approach. Data from the eight most widely quoted trials are summarized in Table 2. It can be seen that several drug combinations have been tested, but in only five of these eight studies has the number of patients entered exceeded 100. It is noticeable that both the overall response rates and the complete remission rates in these randomized studies were considerably lower that those reported in the earlier pilot studies and the most disappointing observation is that there has

Presented at the 16th International Congress of Chemotherapy, Jerusalem, Israel, June 11–16, 1989.

Accepted for publication 3 October 1989.

**Table 1**

*Pilot studies of initial chemotherapy*

| Drugs used | No. of patients by stage | | Response rate (%) | | Survival figures | References |
|---|---|---|---|---|---|---|
| | III | IV | Total | CR | | |
| CDDP + FU | 21 | 48 | 78 | 33 | 50% at 28m | Kies et al. (1) |
| CDDP + FU | 15 | 25 | 83 | 38 | 64% at 12m | Al-Sarraf et al. (2) |
| CDDP + FU | 6 | 25 | 84 | 23 | 59% at 22m | Amrein & Weitzman (3) |
| CDDP + BLM | 11 | 40 | 69 | 24 | 78% at 10m | Haines et al. (4) |
| MTX + FU | 2 | 15 | 78 | 22 | 50% at 19m | Perry et al. (5) |
| MTX + BLM + CDDP | 51 | total (+II) | 59 | 33 | 53% at 36m | Bonheim & Spoendlin (6) |
| MTX + BLM + CDDP | 13 | 15 (+2II) | 90 | 7 | 50% at 15m | Adelstein et al. (7) |
| MTX + BLM + CDDP | – | 14 | 93 | 7 | 50% at 11m | Sridhar et al. (8) |
| MTX + BLM + CDDP | 19 | 95 | 78 | 26 | 50% at 24m | Ervin et al. (9) |
| MTX + BLM + CDDP | – | 70 | 53 | 3 | 26% at 60m | Villar et al. (10) |
| BLM + MTX + VLB + CDDP | – | 11 | 82 | 36 | 82% at 12m | Gonzalez et al. (11) |
| VCR + MTX + BLM + 5FU | 96 | 71 | 65 | ns | 50% at 24m | Price & Hill (12) |

BLM = bleomycin; CDDP = cisplatin; FU = 5-fluorouracil; MTX = methotrexate; VCR = vincristine; VLB = vinblastine; ns = not stated; CR = complete response.

been no reported increase in overall survival. However, in assessing these data it is important to remember that the results of these randomized studies may well have been compromised by the following factors:

a) Use of chemotherapy of limited activity and duration. For example, in certain of these studies only low doses of drugs were administered for less than one month and one of the studies employed only a single agent;

b) Inadequate patient accrual, with less than 100 patients entered in five of the eight trials;

c) Inadequate stratification and balancing of groups; and

d) Suboptimal local-regional treatment following initial chemotherapy.

So, two main conclusions can be drawn from the present investigations of the use of the 'sequential' approach with adjuvant therapy of head and neck cancer, namely that suboptimal trials yield suboptimal results, and secondly that the role of initial chemotherapy in the treatment of head and neck cancer still remains to be defined.

The second series of adjuvant trials has involved the 'simultaneous' approach, utilizing chemotherapy alternating with or given during radiation therapy. Initial evaluation of this approach indicated significantly increased toxicities compared with the 'sequential' approach, but with improved knowledge as to how to ameliorate these side effects a number of randomized studies have been set up. Data from the eight main ones are summarized in Table 3. It should be noted that, in general, single agents only have been tested and the number of patients evaluated has again

**Table 2**

*Randomized controlled trials of initial chemotherapy*

| Drugs used | No. of patients | Response rate CR + PR % | Overall survival benefit | References |
|---|---|---|---|---|
| VCR + BLM + MTX + FU + HU + MP | 86 | ns | None | Stell et al. (13) |
| CDDP + BLM + VCR | 146 | 20 + 25 | Not expected | Schuller et al. (14) |
| MTX | 95 | 6 + 34 | None | Taylor et al. (15) |
| MTX | 60 | 5 + 68 | None | Rentschler et al. (16) |
| BLM + CYCLO + MTX + FU | 83 | 5 + 63 | None | Kun et al. (17) |
| CDDP + BLM + MTX + FU | 60 | 7 + 57 | None | Martin et al. (18) |
| CDDP + FU | 60 | 19 + 67 | None | Toohill et al. (19) |
| CDDP + BLM | 462 | 3 + 34 | None | Head & Neck Contract (20) |

CYCLO = cyclophosphamide; HU = hydroxyurea; MP = 6-mercaptopurine; PR = partial response.
See also footnote to Table 1.

**Table 3**

*Randomized trials of simultaneous chemotherapy plus radiotherapy versus radiotherapy alone*

| Drugs used | No. of patients | Response benefit | Survival benefit | References |
|---|---|---|---|---|
| HU | 125 | None | None | Stefani et al. (21) |
| FU | 155 | ns | Yes, chemo arm | Gollin et al. (22) |
| BLM | 145 | Yes, chemo arm | Yes, chemo arm | Shanta & Krishnamurthi (23) |
| BLM | 224 | None | None | Cachin et al. (24) |
| BLM | 32 | Yes, chemo arm | ns | Kapstad et al. (25) |
| MTX | 313 | | OS better in oropharynx | Gupta et al. (26) |
| MMC | 120 | Yes, chemo arm | DFS, chemo arm | Papac et al. (27) |
| BLM + MTX | 104 | Yes, chemo arm | DFS, chemo arm but not OS | Fu et al. (28) |

DFS = disease-free survival; HU = hydroxyurea; MMC = mitomycin C; OS = overall survival.
See also footnote to Table 1.

been small in certain of the trials. However, four of these eight studies have provided evidence of a response benefit for the chemotherapy arm. Furthermore, what is even more encouraging is that five of these trials report survival advantage, be it in terms of disease-free survival rather than overall survival benefit. One may therefore be encouraged by these data, but it is also important to remember that the results of these randomized studies may have been compromised by:

a) Use of suboptimal chemotherapy. For example, none of the studies has evaluated cisplatin although a number of non-randomized studies, summarized by Choksi et al. (29) recently, utilizing simultaneous chemo-radiotherapy with cisplatin with or without 5-fluorouracil have reported very high complete remission rates of 52 to 94%;

b) Use of suboptimal radiotherapy; and

c) Small numbers of patients in some of the trials.

So the main conclusion from surveying the literature is that use of the 'simultaneous' approach in the treatment of head and neck cancer needs further evaluation. Results of a large randomized trial being carried out by the Head and Neck Intergroup in the USA testing radiotherapy alone versus cisplatin plus radiotherapy are therefore awaited with interest.

In general, all the studies already carried out attempting to assess the role of adjuvant chemotherapy in the treatment of head and neck cancer have led to the conclusion that suboptimal trials yield suboptimal results and that the role of chemotherapy in the treatment of advanced head and neck cancer remains still to be defined.

It is now widely accepted that a randomly assigned, controlled trial, using a protocol with acceptable toxicity and good patient compliance is required for the definitive evaluation of chemotherapy in the management of patients with advanced squamous cell carcinomas of the head and neck. However, it is recognized that results from uncontrolled studies can provide early estimates of the merits of such treatment and knowledge of the variables which must be considered in the proper design of subsequent phase III clinical studies. This was the approach we adopted when in 1975 we were first considering setting up studies to evaluate the role of chemotherapy as adjuvant therapy in the treatment of advanced head and neck cancer. The aim of our study was to establish an initial combination chemotherapy protocol with a high response rate after two courses and minimal toxicity, which could be safely integrated with subsequent local therapy. We are indebted to Mr Henry Shaw and Dr Vera Dalley for referring patients into the study which was carried out at the Royal Marsden Hospital, London, UK, between January 1975 and July 1982. The chemotherapy schedule used became known as Price–Hill Schedule A and consisted of a 4-drug combination of vincristine, bleomycin, methotrexate and 5-fluorouracil given together with hydrocortisone and administered over a 24-h period, followed by a standard folinic acid rescue (see Fig. 1). Full details of the kinetic rationale used in designing this protocol have been provided previously (30, 31). The plan of the study was for patients to receive one course of Schedule A on day zero, the second on day 14 and on day 28 they were assessed for chemotherapy response and curative local therapy was instigated. In this

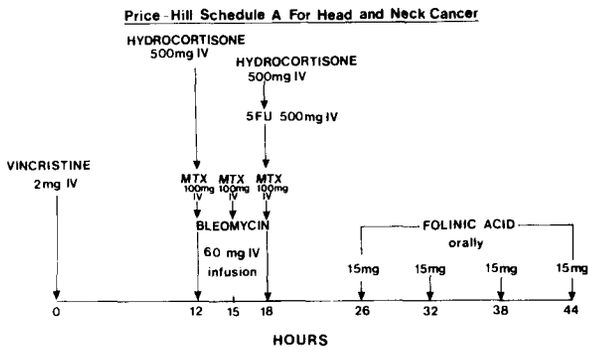


Fig. 1. Price–Hill Schedule A combination chemotherapy protocol for head and neck cancer.

pilot study, 208 patients were entered and response to initial Schedule A chemotherapy was assessed in 200 (32). One hundred and thirty-two patients were judged to be chemotherapy responders, with an overall response rate of 66%. The remaining 68 patients were judged as chemotherapy non-responders, although 19 of these had a minimal 20–30% response to initial chemotherapy when assessed on day 28. One of the main characteristics of this particular Schedule A chemotherapy protocol was the minimal toxicity associated with its administration. Indeed, when the incidence of side effects from 429 treatment cycles of Schedule A chemotherapy given to 208 eligible patients was quantitated, 126 patients (61%) had no side effects at all (32, 33). In the remaining 39% of patients treated there were some side effects and these are listed in Table 4. It is apparent that there was minimal toxicity associated with Schedule A chemotherapy, with the incidence of none of the listed side effects exceeding 10%. There were, however, two deaths which were associated with protocol violations since the standard medical precautions (see Table 5) were not adhered to: one patient with impaired renal function was not given a prolonged folinic acid rescue and one patient was treated with a second course of chemotherapy when their white blood cell count was 3 000 per $mm^3$, but their normal white cell count was 10 000 per $mm^3$. So, provided these standard medical precautions were always observed, this chemotherapy protocol could be administered safely with minimal toxicity and 100% patient compliance. Indeed, the lack of toxicity associated with this particular protocol is remarkable in comparison with a number of the other predominantly cisplatin-containing protocols which were used in subsequent pilot studies, after our study began, from the late 1970s to the early 1980s (see Table 6). Clearly, the advantages in terms of toxicity for this Price–Hill Schedule are that the patient spends only two days on treatment per course, there was only a 10% incidence of nausea and vomiting, a 2% increase of significant myelotoxicity and

**Table 4**

*Incidence of side effects from 429 treatment cycles of Schedule A chemotherapy given to 208 eligible patients*

| Side effects | No. of cycles (%) | No. of patients |
|---|---|---|
| Myelosuppression (wbc < 3 000 per $mm^3$) | 7 (2%) | 5 (2%) |
| Mucositis (mild—no intubation required) | 25 (6%) | 17 (8%) |
| Nephrotoxicity | 0 | 0 |
| Peripheral neuropathy | 12 (3%) | 10 (5%) |
| Pulmonary (chest pains) | 2 | 2 |
| Skin rash | 27 (6%) | 16 (8%) |
| Alopecia | 16 (4%) | 14 (7%) |
| Nausea and vomiting | 26 (6%) | 18 (9%) |
| Anorexia | 5 (1%) | 3 (1%) |
| General malaise and lethargy | 17 (4%) | 8 (4%) |
| Deaths (protocol violations) | 2 | 2 |

**Table 5**

*Standard medical precautions to be observed routinely when administering Schedule A combination chemotherapy*

1. All patients should be carefully examined clinically and have had full haematologic and biochemical profiles recorded.
2. Another treatment cycle should never be given unless the peripheral blood count had returned to its original level. If in doubt, treatment should be postponed for one week.
3. Patients with impaired renal function must be given a proportionately extended folinic acid rescue.
4. All patients must be hydrated so as to produce a urinary output of at least 2 l over the 24-h treatment period. Patients with cardiovascular disease should be given frusemide intravenously at the end of the bleomycin infusion.
5. Bleomycin should be omitted from the second course, if it produced an acute reaction after the first treatment.
6. Patients with a history of chronic respiratory disease should be investigated for a diffusion defect. If one was found, bleomycin should be omitted from the schedule.

**Table 6**

*Summary of toxicities from early studies using cisplatin-containing protocols compared with Price–Hill Schedule A chemotherapy*

| Drugs used | Days on treatment per course | Nausea and vomiting % | Significant myelotoxicity % | Renal toxicity % | References |
|---|---|---|---|---|---|
| CDDP + VCR + BLM | 5 | 71 | 27 | 10 | Al-Sarraf et al. (34) |
| CDDP + BLM | 9 | moderate | 2 | 9 | Hong et al. (35) |
| CDDP + BLM | 9 | 100 | 5 | 20 | Pennachio et al. (36) |
| CDDP + VCR + BLM | 7 | 100 | 2 | 19 | Spaulding et al. (37) |
| CDDP + FU | 4 | 66 | 37 | 22 | Decker et al. (38) |
| CDDP + BLM + MMC | 5 | 100 | 2 | 0 | Israel et al, (39) |
| VCR + BLM + MTX + FU + HC | 2 | 10 | 2 | 0 | Hill et al. (33) |

HC = hydrocortisone; MMC = mitomycin C.
See also footnote to Table 1.

no renal toxicity, contrasting with the high figures for nausea and vomiting and renal toxicity associated with the cisplatin-containing protocols.

In our study, after the patients had received two courses of Schedule A chemotherapy, they went on to local therapy and after completion were judged as to whether they had achieved a complete remission or still had residual disease. At this assesment the overall complete response rate was judged as 69%, with higher rates seen in patients with 'bad risk' stage II and stage III disease, namely 84% and 74%, than those with more advanced stage IV disease, where the complete remission rate was only 49%. Detailed analyses of our data from this large patient series (32, 40) showed that primary tumour site was a significant predictive factor both for response to treatment and for survival. Predictive factors were identified, first for chemotherapy response, using logistic regression on the overall data set. Tumour site was highly significant ($p < 0.001$) and the response rates to initial chemotherapy by site are shown in Table 7. The highest response rates of 80% and 95% were observed in patients with oral cavity and nasopharyngeal tumours respectively. Identifying predictive factors for achieving a final complete remission using logistic regression analyses the following proved significant: chemotherapy response $p < 0.001$, nodal status $p < 0.001$, stage of disease $p < 0.001$, and again, tumour site $p < 0.001$. Highest final complete remission rates were observed (see Table 7) in patients with oral cavity lesions (78%), tumours of the nasopharynx (85%) and larynx (81%). When predictive factors for overall survival were analyzed, multivariate analyses showed superior survival in patients with tumours of the larynx, nasopharynx and oropharynx versus those with oral cavity and hypopharyngeal tumours, with $p < 0.001$. The full actuarial survival curves, provided in Fig. 2, clearly indicate the improved survival figures for patients with nasopharyngeal and laryngeal tumours contrasting with those with tumours of the oral cavity and hypopharynx. Median overall survival figures analysed by site are also shown in Table 7. These illustrate that the high final complete remission rates in patients with tumours of the nasopharynx and larynx were translated into the longest overall survival figures. In contrast, patients with oral cavity tumours who achieved a high complete remission rate had poor median survival figures. This serves to emphasize an important point, namely that a high response rate to initial chemotherapy and achievement of a high final complete remission rate does *not automatically* translate into prolonged good quality survival.

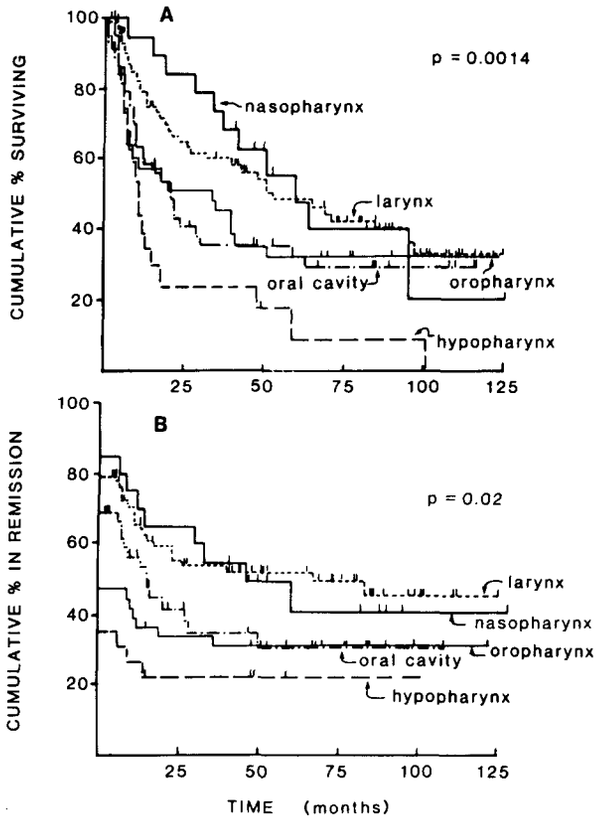


Fig. 2. All patients received two courses of initial Schedule A combination chemotherapy prior to definitive local therapy. A) Actuarial survival analyses by tumour site for all patients, and B) Relapse-free survival analyses by tumour site for all patients. (Reproduced from S. E. Salmon, Ed. 'Adjuvant Therapy of Cancer V' Orlando, Florida: Grune & Stratton 1987; 111–8, with the publishers' permission.)

**Table 7**

*Detailed analyses by site in terms of chemotherapy response, final complete remission rates and median overall survival figures*

| Tumour site | Chemotherapy response rates* | Final CR rates* | Median overall survival (months) |
|---|---|---|---|
| Oral cavity | 36/45 (80%) | 31/40 (78%) | 21 |
| Oropharynx | 20/36 (56%) | 17/35 (49%) | 34 |
| Nasopharynx | 19/20 (95%) | 17/20 (85%) | 60 |
| Hypopharynx | 10/21 (48%) | 8/22 (36%) | 11 |
| Larynx | 41/67 (61%) | 58/72 (81%) | 53 |
| Other miscellaneous sites | 6/11 (55%) | 6/10 (60%) | — |
| | $p < 0.001$ | $p < 0.001$ | $p = 0.0014$ |

* Data obtained from references 32 and 40

From this large pilot study involving 208 patients, therefore, it was possible to conclude:

a) It is feasible to obtain a high response rate of 66% to two courses of initial Schedule A chemotherapy. This result was achieved at the expense of minimal toxicity and minimal interference with the patients' quality of life;

b) Primary tumour site proved a significant predictive factor both for response to treatment and survival;

c) Response to chemotherapy was a favourable prognostic factor for patients with tumours of the nasopharynx, but not for those with oral cavity lesions;

d) Achievement of a final complete remission was a good prognostic sign for patients with tumours of the nasopharynx, or larynx but not for those with oral cavity tumours; and

e) Relapse-free survival and overall survival data proved significantly superior in patients with tumours of the nasopharynx or larynx, compared with other sites.

Overall, therefore, we agree that to clearly define the role of chemotherapy in head and neck cancer, randomized studies are essential. However, our experience suggests that these trials must involve either sufficient numbers of patients for detailed site-by-site analyses or should be designed so as to evaluate specific tumour sites within the head and neck region. We consider that our study serves to illustrate the potential value of carrying our pilot studies since it has enabled a number of significant prognostic factors to be identified for further evaluation in randomized phase III studies. To illustrate this point further, since this was such a large pilot study, we were able to carry out detailed subset analyses. Seventy-three of the patients treated had laryngeal carcinomas and when the predictive factors for survival were analysed in this particular subgroup of patients it was found that the type of local therapy used did not significantly influence either overall or relapse-free survival (see Table 8). These retrospective analyses therefore suggest that the use of this initial Schedule A (Price–Hill) chemotherapy followed by definitive radiotherapy may eliminate the need for radical surgery, so preserving the larynx in patients with advanced disease, a factor which will significantly improve their quality of life. This finding for laryngeal cancer has now been reported in other pilot studies and is currently being tested in a large randomized trial set up by the Veterans Administration Cooperative Study Programme (29), in which patients are randomized to receive either surgery following radiotherapy or chemotherapy followed by radiation. Interim survival data presented recently (43) showed no significant difference at two years in terms of relapse-free survival or overall survival. These authors therefore concluded that induction chemotherapy and radiotherapy with larynx preservation appear to be as effective as surgery and postoperative radiotherapy for advanced laryngeal cancer, without compromise of survival. They do, however, emphasize that further long-term follow-up is necessary before a definitive conclusion can be drawn.

**Table 8**

*Median duration of survival in months after a median follow-up of 8 years utilizing Price–Hill Schedule A as initial combination chemotherapy*

| Local therapy | Overall survival | | Relapse-free survival |
|---|---|---|---|
| | All patients | Uncensored group | Uncensored group |
| Radiotherapy only | 71 | <120 | 107 |
| Surgery and radiotherapy | 51<br>p = 0.38 | 69<br>p = 0.48 | 67<br>p = 0.43 |

It is interesting now to look back at some of the early pilot studies, involving the use of initial chemotherapy, since long-term follow-up data are available. Data from the main studies, summarized in Table 9, show that whilst there is one report of a 5-year survival rate of only 17%, the overall figures in the other studies range from 23 to 44%. Furthermore, as shown in Fig. 3, the recurrence-free survival figure for patients achieving a final complete remission in our study, utilizing Price–Hill Schedule A chemotherapy, has not yet reached 50% after 10 years of follow-up. Clearly this is the subset of patients that it is

**Table 9**

*Impact of initial chemotherapy on survival: Long-term follow-up data*

| Drugs used | No. of patients | Complete remission rates and survival data | References |
|---|---|---|---|
| CDDP + BLM + VLB mainly 3 courses | 64 | CR to chemotherapy = 52%<br>at 5 years 17% alive NED | Perry et al. (44) |
| CDDP + BLM + MTX | 107 | CR to chemotherapy = 26%<br>at 5 years 44% alive NED | Picker et al. (45) |
| BLM ± CDDP or CDDP only | 104 | Final CR = 55%<br>at 5 years 23% alive NED | Karp et al. (46) |
| CDDP + FU 2 courses | 26 | Final CR = 85%<br>at 5 years 30% alive NED | Al-Sarraf et al. (47) |
| CDDP + FU 3 courses | 88 | Final CR = 42%<br>at 5 years 33% alive NED | Al-Sarraf et al. (47) |
| VCR + BLM + MTX + FU 2 courses | 200 | Final CR = 69%<br>at 5 years 35% alive NED | Hill et al. (33) |

See footnote to Table 1.

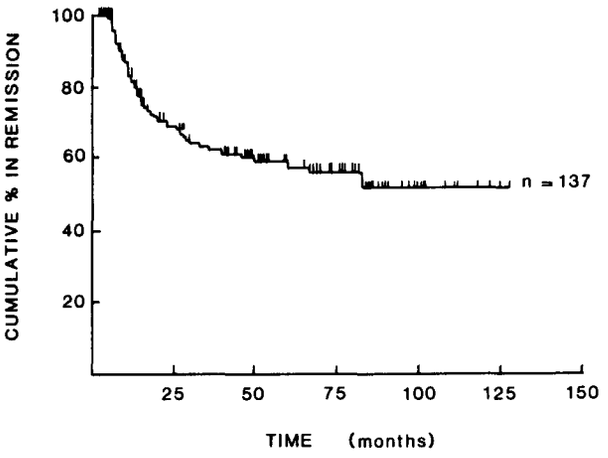


Fig. 3. Overall recurrence-free survival figures for the 137 patients achieving a final complete remission after two courses of initial Schedule A combination chemotherapy followed by definitive local therapy.

essential to identify since they are most likely to benefit from this particular approach.

Therefore, we conclude from our own and other pilot studies that the use of initial induction chemotherapy has established the following positive aspects:

a) Initial chemotherapy is feasible and does not increase surgical or radiotherapy complications;

b) Response rates correlate with tumour burden;

c) Response to chemotherapy predicts subsequent response to radiotherapy;

d) A high complete remission rate is obtainable with an effective regimen;

e) Patients who achieve a complete remission have lengthened survival times; and

f) Radical surgery may be omitted in patients achieving a pathologic complete remission.

However, these initial induction chemotherapy studies have also revealed some negative aspects:

a) Chemotherapy prolongs an already lengthy treatment course;

b) Patients may refuse to undergo local therapy after a good response to initial chemotherapy;

c) Later palliative chemotherapy, if necessary, may be compromised, perhaps, through the development of drug resistant tumour cell populations; and

d) There has, as yet, been no improvement in survival rates in any of the randomized trials, although an optimal trial remains to be carried out.

Finally, future directions in assessing the role of chemotherapy in head and neck cancer may be summarized as follows:

1. It is essential to optimize the activity of combination chemotherapy regimens. In this respect it may be necessary to consider totally new approaches such as the use of intensive high doses of chemotherapy with autologous bone marrow or to consider combining cytotoxic agents with the interferons, interleukins or retinoids. However, before attempting these new types of therapy it may well be possible to improve the chemotherapy protocols already in use, for example, by adding bleomycin to the frequently used combination of cisplatin plus 5-fluorouracil, by increasing the doses of methotrexate and 5-fluorouracil used, or by adding cisplatin to the Schedule A Price–Hill regimen (see Fig. 4).
2. The optimal duration and scheduling of chemotherapy with surgery or radiotherapy must be clarified. In other words, a decision is needed as to whether to adopt the 'sequential' or the 'simultaneous' approach. In this regard, it is possible to utilize the Price–Hill Schedule A alternating with radiotherapy as demonstrated by two groups (48, 49).
3. It is essential to minimize the toxicity of all the combination chemotherapy protocols and enhance patient compliance. This can be achieved using the Price–Hill method, giving the drugs over 24 h with adequate hydration and high-dose antiemetic premedication.
4. We need to identify patients who may successfully receive less local and regional treatment after a response to initial chemotherapy.

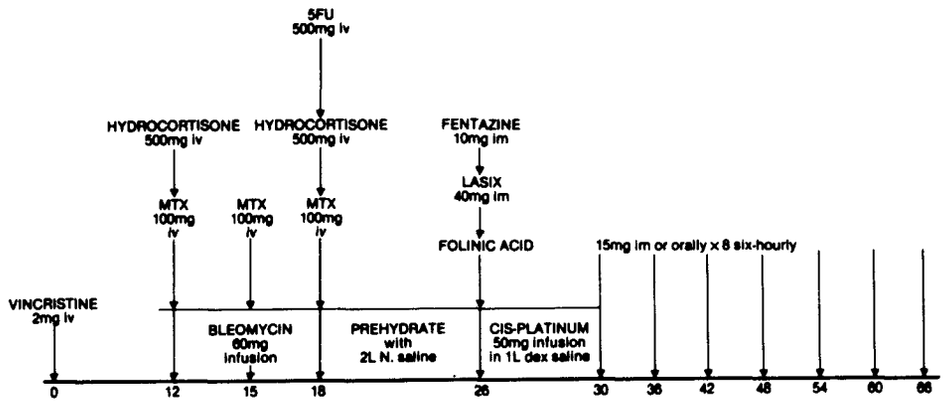


Fig. 4. Combination chemotherapy protocol for advanced head and neck cancer consisting of Price–Hill Schedule A with the addition of cisplatin.

5. We need to identify patients at high risk of relapse who may benefit from additional adjuvant chemotherapy after surgery and/or radiotherapy.
6. Site-by-site analysis is essential in large randomized controlled studies if survival benefits are to be defined.

In conclusion, we consider that considerable progress has already been made in defining an optimal approach to the multidisciplinary treatment of head and neck cancer with chemotherapy. Such efforts should stimulate a new generation of randomized trials, accruing large patient numbers that will permit an accurate assessment of the impact of clearly defined chemotherapy protocols, optimized for received dose intensities, on the natural history of this heterogeneous group of tumours arising within the head and neck region.

*Request for reprints:* Dr. Bridget T. Hill, Cellular Chemotherapy Laboratory, Imperial Cancer Research Fund, Lincoln's Inn Fields, London WC2A 3PX, England.

## REFERENCES

1. Kies Ms, Lester EP, Gordon LI, Blough RR, Gongol J. Taylor SG IV. Cis-platin and infusion 5-fluorouracil in stage III and IV squamous cancer of the head and neck. Proc Am Soc Clin Oncol 1988; 4 (Abstract): 139.
2. Al-Sarraf M, Pajak T. Laramore G. Timing of chemotherapy as part of definitive treatment for patients with advanced head and neck cancer. An RTOG study. Proc Am Soc Clin Oncol 1985; 4 (Abstract): 141.
3. Amrein PC, Weitzman SA, Treatment of squamous cell carcinoma of the head and neck with cisplatin and 5-fluorouracil. J Clin Oncol 1985; 3: 1632–9.
4. Haines I, Bosl G, Pfister D, et al. Very-high-dose cisplatin with bleomycin infusion as initial treatment of advanced head and neck cancer. J Clin Oncol 1987; 5: 1594–600.
5. Perry DJ, David RK, Duttenhaver Jr, et al. Multimodality therapy for unresectable squamous cell carcinoma of the head and neck. Am J Clin Oncol 1985; 100: 380–3.
6. Bonheim K, Spoendlin H. Three-year results of combined modality therapy in locally advanced resectable squamous cell carcinoma of the head and neck. Acta Oto-Laryngol 1985; 100: 134–9.
7. Adelstein DJ, Hines JD, Sharan VM, et al. Combination chemotherapy prior to definitive local therapy in squamous cell carcinoma of the head and neck. Oncology 1985; 42: 80–5.
8 Sridhar KS, Ohnuma T, Biller H, Holand JF, Ambinder EP, Barba J. Combination chemotherapy with high-dose methotrexate, bleomycin, and cisplatin in management of head and neck squamous cell carcinoma. Am J Clin Oncol 1985; 8: 55–60.
9. Ervin TJ, Clark JR, Weichselbaum RR, et al. An analysis of induction and adjuvant chemotherapy in the multidisciplinary treatment of squamous cell carcinoma of the head and neck. J Clin Oncol 1987; 5: 10–20.
10. Villar A, Pera J, Arellano A, et al. Induction chemotherapy with cisplatin, bleomycin and methotrexate in advanced head and neck cancer—lack of therapeutic gain. Radiother Oncol 1987; 10: 175–81.
11. Gonzalez MF, Vadivieso JG, Sartiano GP. Continuous intravenous infusion combination chemotherapy for head and neck squamous cell carcinoma. Oncology 1984; 41: 377–82.
12. Price LA, Hill BT. Impact of primary site of stage III and IV squamous cell carcinomas of the head and neck on 7-year survival figures following initial non-cisplatin-containing combination chemotherapy. Recent Results Cancer Res 1986; 103: 124–34.
13. Stell PM, Dalby JE, Strickland P, Fraser JG, Bradley PJ, Flood FM. Sequential chemotherapy and radiotherapy in advanced head and neck cancer. Clin Radiol 1983; 34: 463–7.
14. Schuller DE, Wilson H, Hodgson S, et al. Pre-operative reductive chemotherapy for stage III or IV operable epidermoid carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx, phase III. Proc Int Conf on Head and Neck Cancer. Chemotherapy II. (Abstract) Baltimore, 1984.
15. Taylor SG IV, Applebaum E, Showel JL, et al. A randomized trial of adjuvant chemotherapy in head and neck cancer. J Clin Oncol 1985; 3: 672–9.
16. Rentschler RE, Wilbur DW, Petti GH, et al. Adjuvant methotrexate escalated to toxicity for resectable stage III and IV squamous head and neck carcinomas—a prospective, randomized study. J Clin Oncol 1987; 5: 278–85.
17. Kun LE, Toothill RJ, Holoye PY, et al. A randomized study of chemotherapy for cancer of the upper aerodigestive tract. Int J Radiot Oncol Biol Phys 1986; 12: 173–8.
18. Martin M, Mazeron JJ, Glaubiger D, et al. Neoadjuvant polychemotherapy of head and neck cancer: Preliminary results of a randomized study. Proc Am Soc Clin Oncol 1986; 5 (Abstract): 141.
19. Toohill, RJ, Anderson T, Byhardt RW, et al. Cisplatin and fluorouracil as neoadjuvant therapy in head and neck cancer. Arch Otolaryngol Head Neck Surg 1987; 113: 758–61.
20. Head and Neck Contracts Program. Adjuvant chemotherapy for advanced head and neck squamous carcinoma: Final report of the Head and Neck Contracts Program. Cancer 1987; 60: 301–11.
21. Stefani S, Eells RW, Abbatte J. Hydroxyurea and radiotherapy in head and neck cancer. Results of a prospective controlled study in 126 patients. Ther Radiol 1971; 101: 391–6.
22. Gollin FF, Ansfield FJ, Brandenberg JH, et al. Combined therapy in advanced head and neck cancer: A randomized study. AJR 1972; 114: 83–8.
23. Shanta V, Krishnamurthi S. Combined bleomycin and radiotherapy in oral cancer. Clin Radiol 1980; 31: 617–20.
24. Cachin Y, Jortay A, Sancho H, et al. Preliminary results of a randomized EORTC study comparing radiotherapy and concomitant bleomycin to radiotherapy alone in epidermoid carcinomas of oropharynx. Eur J Cancer 1977; 13: 1389–95.
25. Kapstad B, Bang G, Rennaes S, et al. Combined preoperative treatment with cobalt and bleomycin in patients with head and neck carcinoma—A controlled clinical study. Int J Radiol Oncol Biol Phys 1987; 4: 85–9.
26. Gupta NK, Pointon RCS, Wilkinson PM. A randomized clinical trial to contrast radiotherapy with radiotherapy and methotrexate given synchronously in head and neck cancer. Clin Radiol 1987; 38: 575–81.
27. Papac RJ, Weissberg JB, Sou UH. Prospective randomized trial of radiation therapy (RT) ± mitomycin C (MC) in head and neck cancer. Proc Am Soc Clin Oncol 1987; 6 (Abstract): 126.
28. Fu KK, Phillips TL, Silverberg, et al. Combined radiotherapy and chemotherapy with bleomycin and methotrexate for advanced inoperable head and neck cancer: Update of a northern California Oncology Group randomized trial. J Clin Oncol 1987; 5: 1410–418.

29. Choksi Aj, Dimery IW, Hong WK. Adjuvant chemotherapy of head and neck cancer: The past, the present and the future. Semin Oncol 1988; 15: 45–59.
30. Price LA, Hill BT. A kinetically-based logical approach to the chemotherapy of head and neck cancer. Clin Oncol 1977; 2: 339–45.
31. Price LA, MacRae KD, Hill BT. Integration of safe initial combination chemotherapy (without cisplatin) with a high response rate and local therapy for untreated stage III and IV epidermoid cancer of the head and neck: 5-year survival data. Cancer Treat Rep 1983; 67: 535–9.
32. Hill BT, Price LA, MacRae K. Importance of primary site in assessing chemotherapy response and 7-year survival data in advanced squamous-cell carcinoma of the head and neck treated with initial combination chemotherapy without cisplatin. J Clin Oncol 1986; 4: 1340–7.
33. Hill BT, Price LA, Busby E, MacRae K, Shaw HJ. Positive impact of initial 24-hour combination chemotherapy without cis-platinum on 6-year survival figures in advanced squamous cell carcinomas of the head and neck. In: Jones SE, Salmon SE, eds. Adjuvant therapy of cancer IV. Orlando, Florida: Grune and Stratton, 1984: 97–106.
34. Al-Sarraf M, Drelichman A, Jacobs J, et al. Adjuvant chemotherapy with cis-platinum, oncovin, and bleomycin followed by surgery and/or radiotherapy in patients with advanced previously untreated head and neck cancer: final report. In: Salmon SE, Jones SE, eds. Adjuvant therapy of cancer III. New York: Grune and Stratton, 1981: 145–52.
35. Hong WK, Pennachio J, Shapsay S, et al. Adjuvant chemotherapy with cis-platinum and bleomycin infusion prior to definitive treatment for advanced stage III and IV squamous cell head and neck carcinoma. In: Salmon SE, Jones SE, eds. Adjuvant therapy of cancer III. New York: Grune and Stratton, 1981: 153–60.
36. Pennachio JL, Hong WK, Shapsay S, et al. Combination of cis-platinum and bleomycin prior to surgery and/or radiotherapy compared with radiotherapy alone for the treatment of advanced squamous cell carcinoma of the head and neck. Cancer 1982; 50: 2795–801.
37. Spaulding MB, Kahn A, De Los Santos R, Klotch D, Lore JM. Adjuvant chemotherapy in advanced head and neck cancer: an update. Am J Surg 1982; 144: 432–6.
38. Decker DA, Drelichman A, Jacobs J, et al. Adjuvant chemotherapy with cis-diammino-dichloroplatinum II and 120-hour infusion with 5-fluorouracil in stage III and IV squamous cell carcinoma of the head and neck. Cancer 1983; 51: 1353–5.
39. Israel L, Aquilera J, Soudant J, Penot JC, Brean JL, Morere JF. Bleomycin and cis-platinum with or without mitomycin C in 110 previously untreated patients with head and neck cancer. Am J Clin Oncol 1983; 5: 305–11.
40. Hill BT, Price LA. The significance of primary site in assessing chemotherapy response and survival in advanced squamous cell carcinomas of the head and neck treated with initial combination chemotherapy without cisplatin: Analyses at nine years. In: Salmon SE, ed. Adjuvant therapy of cancer V. Orlando, Florida: Grune and Stratton, 1987: 111–8.
41. Hill BT, Price LA. Use of initial Schedule A combination chemotherapy without cisplatin followed by radiotherapy as definitive local treatment for advanced laryngeal cancer: Ten years follow-up analysis of this non-surgical approach. Proc Am Soc Clin Oncol 1988; 7 (Abstract): 149.
42. Hill BT, Price LA, Love S. Induction combination chemotherapy without cisplatin followed by radiotherapy without radical surgery as definitive treatment for advanced laryngeal cancer. In: Jacquillat C, Weil M, Khayat D, eds. Neo adjuvant chemotherapy, Second International Congress. Collo Inserm. London: John Libbey Eurotext, 1988; 169: 303–8.
43. Hong WK, Wolf GT, Fisher S, et al. Laryngeal preservation with induction chemotherapy and radiotherapy in the treatment for advanced laryngeal cancer: Interim survival data of VACSP No. 268. VA laryngeal cancer study group. Proc Am Soc Clin Oncol 1989; 8 (Abstract): 167.
44. Perry DJ, Davis RK, Zajtchuk JR, Baumann JC. Vinblastine, bleomycin and cisplatin in the treatment of squamous carcinoma of the head and neck. In: Jones SE, Salmon SE, eds. Adjuvant therapy of cancer IV. Orlando, Florida: Grune and Stratton, 1984: 135–43.
45. Picker H, Zingerle N, Boheim K, Lochs A, Spoendlin H. The prognostic influence of induction chemotherapy on advanced head and neck carcinoma. Arch Oto-Rhino-Laryngol 1986; 243: 324–8.
46. Karp DD, Vaughan CW, Willet B, et al. Long-term survival following induction chemotherapy for squamous cell carcinoma of the head and neck: A ten-year follow-up. In: Salmon SE, ed. Adjuvant therapy of cancer V. Orlando, Florida: Grune & Stratton, 1987: 119–27.
47. Al-Sarraf M, Reading B, Kish JA, et al. Adjuvant chemotherapy for patients with locally advanced head and neck cancer: RTOG and Wayne State University experiences. In: Salmon SE, ed. Adjuvant therapy of cancer V. Orlando, Florida: Grune and Stratton, 1987: 89–100.
48. Bezwoda WR, de Moor NG, Derman DP. Treatment of advanced head and neck cancer by means of radiation therapy plus chemotherapy—A randomized trial. Med Paed Oncol 1979; 6: 353–8.
49. Malaker K, Robson F, Schipper H. Treatment of head and neck cancer with split course radiotherapy and combination chemotherapy. In: Jones SE, Salmon SE, eds. Adjuvant therapy of cancer II. New York: Grune and Stratton, 1979: 437–45.