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Review paper

Role of vindesine as neoadjuvant chemotherapy for non-small cell lung and head and neck cancers

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Although surgery is the only therapeutic intervention with potential for cure of non-small cell lung cancer (NSCLC) and head and neck cancer, most patients present with tumors that are too far advanced for resection. For this reason, neoadjuvant chemotherapy is being increasingly used to down-stage primary tumor burden before surgery. The procedure offers the possibility of enhancing resectability and thereby improves the chances of achieving complete eradication. In NSCLC, the most successful results have been obtained in patients with disease that is localized to the thorax and in those achieving complete responses to chemotherapy. A number of different combination regimens have been studied with cisplatin as the key component. Response rates of up to 88% have been reported together with complete sections in up to 74% of patients. The impact on survival is still to be determined. Although there is ample data showing that combination regimens containing vindesine have a favorable effect on survival in patients with inoperable NSCLC, relatively few of the studies have evaluated these regimens for use as neoadjuvant therapy. New studies should focus on increasing the complete response rate above the 20% level that is currently attainable. The results using neoadjuvant chemotherapy in head and neck cancer are disappointing with no survival benefit demonstrated. However, neoadjuvant chemotherapy may help preserve organ function and thus improve quality of life of patients.

Key words: Head and neck cancer, lung cancer, neoadjuvant chemotherapy, vindesine.

Introduction

Surgery offers the only realistic chance of cure for patients with either non-small cell lung cancer (NSCLC) or head and neck cancer. However, the success of surgical intervention is highly dependent on the appropriate selection of patients. Survival rates are related to tumor burden and, when confined to locoregional extent, particularly to lymph node involvement.

In NSCLC, candidates for resection include only those with stage I and II disease[1–3] and a small group of patients with stage IIIa disease in whom the disease is confined to the ipsilateral thorax.[4,5] The 5-year survival in these patients is 25–30%. In many patients with stage IIIa disease, the disease is already locally advanced and surgery is not appropriate. The 5-year survival in these patients is less than 10%.[6]

Long-term survival rates following surgical resection in stage III NSCLC are disappointing. Death in most resected patients is cancer related and follows systemic recurrence.[6] Since results of surgical treatment of lung cancer have been largely unchanged for many years, attention is being focused on the use of pre- or post-operative adjuvant radiotherapy, chemotherapy and immunotherapy.

Almost two-thirds of patients with head and neck cancer have advanced disease (stage III and IV) at diagnosis.[7] The standard treatment for advanced head and neck cancer is surgery and/or radiotherapy depending on whether the tumor is resectable. The prognosis is poor and the typical survival rate is less than 50% at 4 years.

The objective of administering chemotherapy after surgery is to eradicate circulating tumor cells and subclinical metastases not recognized at the time of surgery, and thereby improve disease-free survival rates. Neoadjuvant (induction) chemotherapy, on the other hand, has the added aim to down-stage primary tumor burden that is too far advanced to allow surgery. The procedure is undertaken to enhance resectability, to offer the opportunity of adopting a more conservative surgical approach and/or to improve the chances of achieving complete eradication of tumor burden through radical or complementary radiotherapy.

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Administration of chemotherapy early in the course of the disease offers the possibility of treating subclinical established metastatic disease at the time when chemotherapy is likely to have the greatest impact. This is also the time when the patients are best able to tolerate potential toxicity. Since neoadjuvant chemotherapy involves an assessment of the responsiveness of the primary tumor to pre-operative chemotherapy, it offers the advantage of being able to identify patients who might benefit from further chemotherapy post-operatively.[8]

A putative disadvantage of neoadjuvant treatment is increased surgical morbidity.[8] Theoretical drawbacks include the possibility that early systemic therapy may facilitate the emergence of chemotherapy-resistant tumor cells. It may also delay the point at which effective local tumor control can be achieved, in which case it would increase the risk of metastatic spread. From the surgeon's perspective, successful neoadjuvant therapy has the effect of complicating the decision concerning the extent of surgical resection; from the patient's perspective it tends to compromise willingness to consent to subsequent surgical intervention.

Neoadjuvant chemotherapy in NSCLC

Rationale for neoadjuvant chemotherapy in NSCLC

NSCLC is a moderately chemosensitive malignancy and chemotherapy induces objective regression in patients with advanced disease.[9]

Stage III NSCLC includes patients with a wide range of disease severity. The International Staging System for Lung Cancer uses classifications of T (primary tumor), N (nodal involvement) and M (distant metastases).[10] Stage III locally advanced NSCLC can be defined using this classification (Table 1). Classification as stage IIIa disease (potentially curable by surgery) requires the presence of T3 and/or N2 disease. Classification as stage IIIb disease (virtually incurable) requires the presence of T4 and/or N3 disease.

However, within stage IIIa N2 itself, there is considerable variation in nodal involvement and this is a particularly important prognostic factor for outcome after surgery.[8] If there is only microscopic involvement of the mediastinal node (minimal involvement) the prognosis is good compared with patients who have more than one lymph node involved (non-minimal involvement). Therefore, neoadjuvant chemotherapy is proposed for patients in this latter category to improve the outcome after surgery.

Pre-operative chemotherapy has been shown to be most successful in patients with disease that is localized to the thorax. A study using combination chemotherapy with cisplatin (120 mg/m^2), vinca alkaloids and mitomycin (MVP) given pre-operatively to patients with stage IIIa NSCLC with clinically apparent ipsilateral mediastinal spread, suggested that major objective responses can be achieved in up to 77% of patients and complete responses in approximately 10% of patients.[11] Overall, 60% of this study population were able to undergo complete resections and 12% had complete response at surgery. The median survival was 19 months for all patients and 27 months for the resected patients. Interestingly, the 3-year survival rate among resected patients (44%) was significantly higher than that achieved with surgery alone (8%).[12]

Comparison of neoadjuvant chemotherapy plus surgery with surgery alone

Two prospective phase III randomized studies have demonstrated that survival of patients with stage III

Table 1. Classification of stage III NSCLC: IIIA disease must involve T3 and/or N2, IIIB disease must involve T4 and/or N3

	Stage IIIa	Stage IIIb
Primary tumor	T3: Tumor of any size with extension into the chest wall, diaphragm mediastinal pleura, pericardium. Tumor in the main bronchus more than 2.0 cm distal to the carina. Associated atelectasis or obstructive pneumonitis of the entire lung.	T4: Tumor of any size with invasion of mediastinum, heart, great vessels, trachea, esophagus, vertebral body or carina. Tumor with malignant pleural effusion.
Nodal involvement	N2: Metastasis to ipsilateral mediastinal and/or subcarinal lymph nodes.	N3: Metastases to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes.
Distant metastases	M0: No distant metastases.	M0: No distant metastases.

Table 2. Studies comparing neoadjuvant chemotherapy plus surgery with surgery alone

Reference	Stages	Pre-operative treatment	No. of patients	Response rate (CR+PR)	Complete resections	Median survival
17	I II III	DDP+CPM+VDS+surgery	13	5/11 (45%)	11/13 (84%)	20 months
	T1 T2 T3	Surgery	13	–	13/13 (100%)	23 months
	N0 N1 N2					
16	I II IIIA	VP16+DDP+surgery	13	8/13 (62%)	11/13 (85%)	ND
	T2 T3	Surgery	14	–	12/14 (79%)	ND
	N2					
13	IIIA	DDP+VP16+CPM+surgery	26	9/26 (35%)	11/28 (39%)	64 months
	T1 T2 T3	Surgery	32	–	10/32 (31%)	11 months
	N0 N1 N2					
14	IIIA	MTC+DDP+IFO+surgery	30	18/30 (60%)	23/27 (85%)	26 months
	T1 T2 T3	Surgery	30	–	27/30 (90%)	8 months
	N0 N1 N2					
15	I II IIIA	MTC+IFO+DDP+surgery	54	ND	43/49 (88%)	ND
		Surgeryu	63	–	51/62 (82%)	ND

ND, not determined; DDP, cisplatin; MTC, mitomycin; VDS, vindesine; VP16, etoposide; 5-FU, 5-fluorouracil; CPM, cyclophosphamide; IFO, ifosfamide.

disease is longer in patients receiving neoadjuvant chemotherapy before surgery than in patients undergoing surgery alone[13,14] (Table 2).

Roth *et al.* randomized 60 patients to receive either neoadjuvant chemotherapy and surgery or immediate surgical resection alone.[13] Neoadjuvant chemotherapy consisted of cyclophosphamide (500 mg/m^2), etoposide (100 mg/m^2) and cisplatin (100 mg/m^2). The response rate to neoadjuvant chemotherapy was 35% (one complete response and eight partial responses). A further 31% of patients had tumor shrinkage. A total of 61% of patients in the neoadjuvant chemotherapy group and 66% of patients in the surgery only group had resectable disease, and complete resections were possible in 39 and 31% of patients, respectively. There were no differences between the chemotherapy plus surgery group and the surgery only group in respect of post-operative complications (10 versus 6%) and operative deaths (0 versus 6%).

There was a statistically and clinically significant difference in survival between the two treatment groups. The estimated median survival in the neoadjuvant chemotherapy group was 64 months compared with 11 months in the surgery only group. Six patients in the neoadjuvant chemotherapy group were alive and disease-free 3 years later. Only one patient in the surgery group was still alive.

In the second study,[14] 60 patients were randomized to either neoadjuvant chemotherapy with mitomycin (6 mg/m^2), ifosfamide (3 g/m^2) and cisplatin (50 mg/m^2) followed by surgery, or surgery alone. A total of 60% of patients receiving neoadjuvant chemotherapy achieved a response (16 complete responses and two partial responses) and 85% of these patients underwent complete resection. In the surgery only group, 90% of patients underwent complete resection. As in the study by Roth *et al.*, there were statistically and clinically significant differences in survival.[13] Disease-free and overall survival in the surgery group were 5 and 8 months, respectively, compared with 20 and 26 months, respectively, in the neoadjuvant chemotherapy group. The improved outcome with neoadjuvant chemotherapy compared with surgery alone caused both these randomized trials to be closed early.

These two studies suggest that longer-term survival is a possibility for patients with stage IIIA NSCLC. Two further randomized studies are in progress using neoadjuvant chemotherapy regimens of either mitomycin, ifosfamide and cisplatin[15] or etoposide and cisplatin[16] compared with surgery only. Interim results support the studies by Roth and Rosell, indicating that neoadjuvant chemotherapy increases the number of patients who are able to undergo complete resection. However, survival data is not available yet (Table 2).

A study comparing neoadjuvant chemotherapy (cisplatin, vindesine, cyclophosphamide) with surgery alone was stopped early after evidence of pre-operative progression in the chemotherapy arm[17] (Table 2). This emphasizes the importance of establishing the optimal neoadjuvant regimen with a high response rate and low progression rate.

Chemotherapy regimens for neoadjuvant treatment

A wide range of chemotherapy regimens has been used in addition to those studied in the randomized trials described above. Cisplatin is a key component and has been combined with many different chemotherapeutic

Table 3. Neoadjuvant treatment studies: chemotherapy

Reference	Stages	Pre-operative treatment	No. of patients	Response rate (CR+PR)	Complete resections	Median survival
57	T2 T3, N2 N3	DDP+VDS+VP16	27	13/23 (56%)	4/23 (17%)	8 months
11	IIIA	DDP+MTC+VDS or VLB	61	56/73 (77%)	44/73 (60%)	27 months
	T1 T2 T3	DDP+VDS or VLB	12			
58	IIIA IIIB T2 T3 T4, N2 N3	DDP+EPI+VP16	20	8/20 (40%)	5/20 (25%)	ND
41	IIIA T1 T2 T3, N2	MTC+DDP+VDS	39	25/39 (64%)	18/39 (46%)	19 months
34	IIIA T1 T2 T3, N2	MTC+DDP+VDS or VLB+DDP	136	105/136 (77%)	89/136 (65%)	19 months
42	IIIA IIIB T3 T4, N1 N2	DDP+5-FU+VP16	35	24/35 (68%)	26/35 (74%)	19 months
18	IIIA IIIB	DDP+VDS or IFO+VP16 or				23 months
	T2 T3 T4	DDP+VP16+IFO	40	21/60 (35%)	22/60 (37%)	responders
	N1 N2 N3	DDP+IFO+VP16+G-CSF	20			
59	IIIA T1 T2 T3, N2	DDP+VP16	46	37/45 (82%)	28/45 (62%)	25 months
43	IIIA IIIB T3 T4, N2	DDP+VP16+IFO	33	23/33 (70%)	18/33 (55%)	10 months
60	IIIA T1 T2 T3, N2	DDP+VLB	74	65/74 (88%)	23/74 (31%)	24 months

ND, not determined; RT, radiotherapy; DDP, cisplatin; MTC, mitomycin; VDS, vindesine; VP16, etoposide; 5-FU, 5-fluorouracil; VLB, vinblastine; ADM, doxorubicin; CPM, cyclophosphamide; IFO, ifosfamide; VRL, vinorelbine; EPI, epirubicin; CBDCA, carboplatin.

drugs including: mitomycin, etoposide, 5-fluorouracil, doxorubicin and cyclophosphamide, as well as the vinca alkaloids vindesine, vinblastine and vinorelbine. A review of non-randomized studies is presented in Table 3. Response rates (complete and partial responses) have been reported of 35–88%. Complete resection rates of up to 74% have been achieved with overall median survivals of up to 27 months. As expected, the best outcomes have been obtained in patients with stage IIIA disease and limited nodal involvement. However, several studies have included patients with stage IIIB disease and complete resections have been possible in a number of these patients.

Fischer *et al.* showed that increasing the dose intensity of neoadjuvant chemotherapy increased the response rate.[18] Patients received either cisplatin/ifosfamide/etoposide (with or without vindesine) at four-weekly intervals or cisplatin/ifosfamide/etoposide at three-weekly intervals supported with granulocyte colony stimulating factor (G-CSF). The response rates were 35 and 60%, respectively. The incidence and severity of neutropenia was lower in patients receiving the regimen with haematopoietic support.

Chemoradiotherapy as neoadjuvant treatment

Combined neoadjuvant radiotherapy and chemotherapy offers the possibility of attaining enhanced local control partly because of the radiosensitizing effects of chemotherapy and partly because of the simultaneous treatment of systemic micrometastases. However, in practice radiotherapy seems to offer little benefit in terms of improving the response rates above those achieved with combination chemotherapy alone (Table 4). In trials investigating pre-operative radiotherapy and cisplatin-based chemotherapy, the response rates were between 39 and 68%. The complete resection rates varied between 18 and 60%, and median survival ranged between 11 and 32 months. Again, patients with stage IIIA and stage IIIB disease were included in these studies, and the complete resection rate of 18% was obtained in a study which included some patients with stage IV disease.

However, Macchiarini *et al.* obtained a response rate of 100% and a complete resection rate of 91% using aggressive neoadjuvant chemotherapy regimens of either mitomycin, cisplatin and vindesine or cisplatin, vinorelbine and 5-fluorouracil or cisplatin and 5-fluorouracil.[19] Some patients also underwent radiotherapy. The 3-year survival was 62% compared with an expected survival of these patients of 14%. The stage of disease, general condition of the patient and the treatment team's experience in the management of aggressive systemic therapy may explain the wide range of results.

It is impossible to accurately assess the risk–benefit ratio for neoadjuvant therapy at the moment. Serious toxicity has been observed in some of the reported

Table 4. Neoadjuvant treatment studies: chemoradiotherapy

Reference	Stages	Pre-operative treatment	No. of patients	Response rate (CR+PR)	Complete resections	Median survival
61	III T1 T2 T3, N0 N1 N2	DDP+5-FU+VP16+ concomitant RT	23	17/23 (84%)	6/23 (26%)	12 months
62	III T1 T2 T3, N1 N2 N3	DDP+ADM+CPM+ concomitant RT	39	20/39 (51%)	13/39 (33%)	11 months
63	III T3, N1 N2 N3	DDP+5-FU+concomitant RT	64	36/64 (56%)	17/64 (26%)	16 months
39	III IV N2 N3	DDP+MTC+VLB± sequential/concomitant RT	31	14/22 (73%)	4/22 (18%)	19 months
64	IIA IIB T3, N2	DDP+5-FU+VIP16+ concomitant RT	33	23/31 (74%)	23/31 (57%)	15 months
44	IA IIIB, mostly N2	DDP+5-FU±concomitant RT	85	48/85 (56%)	24/85 (28%)	13 months
40	IIIA T1 T2 T3, N0 N1 N2	DDP+5-FU+VLB+ concomitant RT	41	19/41 (46%)	24/41 (59%)	16 months
65	IIIA	CBDCA+VP16+concomitant RT	28	13/28 (46%)	12/18 (43%)	ND
19	IIIB T4	MTC+DDP+VDS±sequential RT or DDP+VRL+5-FU± sequential RT or DDP+ 5-FU± concomitant RT	23	23/23 (100%)	21/23 (91%)	ND
38	III T1 T2 T3, N0 N1 N2	DDP+ADM+CPM± sequential RT	41	21/54 (39%)	24/54 (44%)	32 months

ND, not determined; RT, radiotherapy; DDP, cisplatin; MTC, mitomycin; VDS, vindesine; VP16, etoposide; 5-FU, 5-fluorouracil; VLB, vinblastine; ADM, doxorubicin; CPM, cyclophosphamide; IFO, ifosfamide; VRL, vinorelbine; EPI, epirubicin; CBDCA, carboplatin.

studies including deaths from complications of neoadjuvant chemotherapy, severe neutropenia and lung-related toxicity. The addition of radiotherapy may increase morbidity as a result of exacerbating the toxicity of chemotherapy and also because of the toxicity of the radiotherapy itself.

Vindesine as neoadjuvant therapy

The vinca alkaloids vincristine and vinblastine are derived from the Madagascar Periwinkle (*Caranthus roseus*). Vindesine is a semi-synthetic member of this group. The vinca alkaloids exert their anti-tumor action by binding to tubulin units thus preventing their assembly into microtubules in actively dividing cells.[20] As a single agent it yields response rates of around 18% in NSCLC which ranks it among the most active agents in this disease.[20] In addition to its efficacy in the treatment of NSCLC, recent phase II studies have reported objective responses in patients with small cell lung cancer, breast cancer, melanoma, head and neck cancer, acute lymphoblastic leukemia, acute and chronic myeloid leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma.[21]

An increasing number of clinical trials have shown that combination regimens containing cisplatin and vindesine have anti-tumor activity in patients with inoperable NSCLC. However, relatively few of the studies have separated response in pretreated and non-pretreated patients, and fewer still have commented on the outcome of any subsequent surgical resection.

Major objective response rates in studies using vindesine and cisplatin in combination vary between 22 and 35%, with between 4 and 7% of patients achieving a complete response.[22-25] The addition of mitomycin to cisplatin and vindesine increases the major response rates in stage III NSCLC to as high as 60%.[26-28] In one study the response rate doubled from 27 to 54% in patients receiving mitomycin, relative to those receiving cisplatin and vindesine without mitomycin.[28] Complete response rates with these regimens range from 7 to 12%.

In trials investigating the use of the combination chemotherapy with vindesine and mitomycin without cisplatin, response rates were 36% in previously-untreated patients and 17% in previously-treated patients.[29] The pooled single-agent response rate in previously untreated patients with NSCLC is the same with vindesine (17%: 95% CI 13-22%) and mitomycin (17%: 95% CI 9-25%). Combination therapy with vindesine and mitomycin in previously untreated patients resulted in a response rate of 36% which is greater than with either agent alone.[29] These findings agree with those of the Southeastern Cancer Study Group who reported a response rate of 35% in 59

patients with advanced NSCLC treated with vindesine and mitomycin who had not previously received chemotherapy.[30] The results with vindesine and mitomycin are similar to those obtained with mitomycin and vinblastine or vincristine and fluorouracil.[31-33]

These results indicate that vindesine may be a candidate for inclusion in combination chemotherapy regimens for use in neoadjuvant treatment. The combination of vindesine, cisplatin and mitomycin appears to be particularly active (Tables 3 and 4).

Martini *et al.* administered two to three courses of MVP to 136 patients with stage IIIa NSCLC (Figure 1).[34] The overall response rate was 77%, with 13 complete responses. The overall complete resection rate was 65% and the complete resection rate in patients with a major response to chemotherapy was 78%. For patients who had complete resection, the median survival was 27 months and the 3- and 5-year survivals were 41 and 26%. This is higher than in patients treated with resection only.

As described in the previous section, when MVP was used in conjunction with radiotherapy in patients with stage IIIB disease in whom the use of neoadjuvant chemotherapy is controversial, a response rate of 99% was achieved and complete resections were possible in 91% of patients.

Rosell *et al.* compared MVP with vindesine, cisplatin and ifosfamide (IVP) in 103 patients with stage III and IV NSCLC.[35] Vindesine was given as a 3 mg/m^2 i.v. bolus weekly for 5 weeks. Cisplatin (120 mg/m^2) was administered using a modified hydration technique on day 1, day 29 and at 6 week intervals thereafter. Mitomycin 8 mg/m^2 was administered with the first three doses of cisplatin in 53 patients and ifosfamide (3 g/m^2) was administered with the first three doses of cisplatin in 50 patients. Objective responses were observed in 26% of patients receiving MVP and in 20% receiving IVP. The response rate was higher in patients with stage III disease (33%) than in those with stage IV NSCLC (16%), irrespective of the regimen administered. No complete responses were obtained. However, four of the responders who previously had bulky intrathoracic disease underwent lung surgery after achieving partial remission. No residual tumor was found in pathological lung specimens from two of the four cases. One of the two responding patients had an upper lung lobectomy and was well 22 months later. The other had right pneumonectomy but died suddenly 8 days postoperatively as a result of adult respiratory distress syndrome possibly related to the pulmonary toxicity of mitomycin.

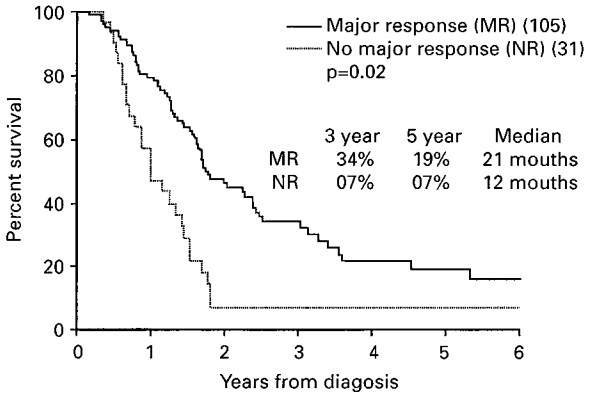

Figure 1. Survival by response to chemotherapy[34] (reproduced with permission).

Vinblastine and vinorelbine have also been included in neoadjuvant chemotherapy regimens (Tables 3 and 4). In several studies they have been used interchangeably with vindesine, and the response rates and resection rates are similar to those achieved with the vindesine combinations.

The responses obtained with chemotherapy based on vindesine and cisplatin combinations need to be weighed against chemotherapy-induced toxicity which may cause early discontinuation of treatment. The major toxicities with these regimens include thrombocytopenia (15%) and leucopenia (30%) which are usually mild with vindesine but are exacerbated by cisplatin.[22-25] Vindesine is also associated with constipation and peripheral neuropathy. In up to 12% of cases neuropathy is severe (WHO grade 3) resulting in paralytic ileus or weakness in extremities which impairs daily activities. The effect is reversible several weeks after stopping treatment, which means that severely affected patients are unable to receive repeat cycles of vindesine-based chemotherapy. Other potential adverse events associated with cisplatin are nephrotoxicity, nausea and vomiting. Both are dose related, and can nowadays be prevented in the vast majority of cases with careful dose selection, hydration and pre-treatment with 5-HT$_3$ anti-emetics. Mitomycin-induced pulmonary toxicity is a serious complication in up to 2% of cases, but can be avoided by limiting the cumulative dose to a maximum of 30 mg/m^2 and pre-medicating with dexamethasone.[36]

Toxicity can be minimized by using low-dose chemotherapy given at frequent intervals. A regimen of 60 mg/m^2 cisplatin, 3 mg/m^2 vindesine and 8 mg/m^2 mitomycin was found to result in a comparable response rate (i.e. 35%) to that achieved with conventional doses of cisplatin and the regimen was associated with a lower incidence of adverse events.[37]

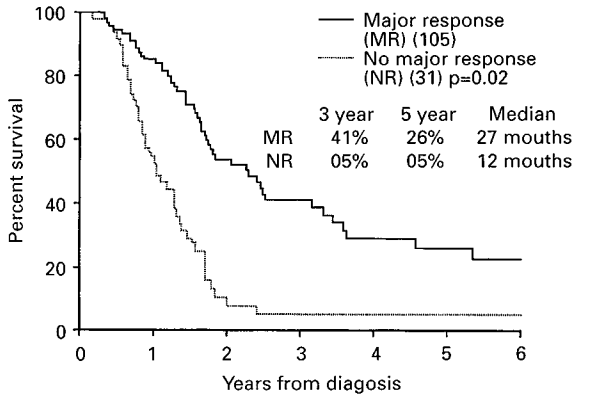

Figure 2. Survival by extent of resection[34] (reproduced with permission).

Prediction of outcome after neoadjuvant chemotherapy

Most of the studies cited in Tables 2 and 3 observed that a response to chemotherapy and complete resection of tumor correlated with survival. For example, when response to chemotherapy was considered, the median survival in patients with a major (complete or partial) response was 21 months, compared with 12 months in patients who did not respond to chemotherapy ($p = 0.02$).[34] The median survival after complete and incomplete resections were 27 and 12 months, respectively ($p = 0.00002$) (Figure 2).

Survival was best in patients who had a complete pathologic response with no residual tumor. Their survival from diagnosis was 95% at 1 year, 71% at 3 years and 61% at 5 years. However, individual prognostic factors for survival after neoadjuvant chemotherapy and surgery were not consistent. Although Martini *et al.* found that patients with T1 or T2 tumors had a significantly longer survival than patients with T3 tumors (23 versus 4% at 5 years, $p = 0.02$)[34] and Elias *et al.* suggested that better survival was associated with absence of or limited nodal involvement,[38] a multiple regression analysis performed by Spain and colleagues found that extent of disease was not a contributing factor.[39]

Two studies reported poorer survival in patients with disease extended to mediastinum.[19,11] In the study by Pisters *et al.*, only 18% of patients with mediastinal disease had a complete resection compared with 44% overall. Strauss *et al.* found a number of adverse prognostic factors present in long-term survivors, including N2 disease with mediastinal involvement.[40] Burkes reported that patients with squamous cell histology fared worse that those with other disease but this was not confirmed across other studies.[41]

In patients who relapsed, recurrence occurred both at local and distant sites. Local recurrence was most common in patients who had had an incomplete resection, whereas distant metastases occurred in patients who had a complete resection.[34] The brain was the main site of distant metastases.[42,43] In the study by Weiden and Piantadosi, disease recurred in 64 of 85 patients.[44] Twenty-nine of these patients had had a complete resection and 28% developed brain metastases compared with 7% who had had an incomplete resection. Administration of prophylactic cranial irradiation[40] prevented the development of subsequent brain metastases. The other sites of metastases were bone, liver and adrenal.

Neoadjuvant chemotherapy in head and neck cancer

Rationale for the use of neoadjuvant chemotherapy in head and neck cancer

No long-term cures have been achieved with chemotherapy in head and neck cancer, but around one-third of patients have a substantial improvement in disease-related symptoms.[45] Cisplatin-based combination chemotherapy regimens produce higher response rates than single-agent treatment, but in various randomized trials, the difference in survival was minimal. From the evidence of higher activity, cisplatin-based regimens may be considered as the standard treatment for recurrent/metastatic disease in patients with good performance status. For patients with poor general condition, single-agent chemotherapy (methotrexate or cisplatin) may be more appropriate.

The development of more active regimens through biochemical modulation or the introduction of new agents (taxoids, vinorelbine, etc.) has resulted in chemotherapy being applied at an earlier stage of the disease, in combination with local treatment, radiotherapy and/or surgery.

Randomized studies of neoadjuvant chemotherapy in head and neck cancer

In patients with locally advanced disease (stage III–IV, M0) treated with surgery and radiotherapy (resectable) or radiotherapy alone (unresectable), disease control can be obtained in 30% or less of cases. The

introduction of more active chemotherapy regimens, such as continuous infusions of cisplatin and 5-fluorouracil, in locally advanced disease have brought about response rates higher than 90%. Complete response rates higher than 50% have been achieved and around half of these are confirmed pathologically.

From the extensive literature on neoadjuvant treatment in head and neck cancer, the current consensus may be summarized as follows:

- Patients with complete histological response have a survival benefit over partial or non-responders.
- Responders to chemotherapy respond to radiotherapy without severe toxicity.
- The incidence of distant metastases is reduced.

During the last few decades, many randomized trials have confirmed these conclusions (Table 5). In most of the trials, although significant response rates were achieved, the difference in overall survival was not significant. The incidence of distant metastases was reduced in some studies. However, the clinical significance of this is unclear.[7] Chemotherapy was combined sequentially with radiotherapy, surgery or both, in resectable and non-resectable disease.

The failure of systemic chemotherapy to influence overall survival may be attributed to problems of:

- Design: incorrect stratification of prognostic factors, insufficient sample size.
- Inadequate local treatment (surgery or radiotherapy) in responding patients.
- Too low frequency and intensity of chemotherapy.

Pacagnella compared four cycles of cisplatin (100 mg/m^2 on day 1) and 5-fluorouracil (1000 mg/m^2 on days 1-5) followed by locoregional treatment (surgery and/or radiotherapy) with locoregional treatment alone, in patients with advanced non-metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx and paranasal sinuses.[46] When all 237 randomly assigned patients were analyzed, there were no significant differences between the two treatment strategies in terms of locoregional failure, or in disease-free or overall survival. Interestingly, when 171 inoperable patients from both treatment arms were analyzed, neoadjuvant chemotherapy, compared with local treatment alone, decreased the incidence of distant metastases (78 versus 86% at 3 years) and improved the complete remission rate (44 versus 30%) and overall survival (24 versus 10% at 3 years).

Vindesine as neoadjuvant chemotherapy in head and neck cancer

The activity of vindesine as a single agent in patients with head and neck cancer is limited. Response rates have varied from 0% in previously treated patients to 25% in chemotherapy-naive patients.[21] Higher response rates have been achieved when vindesine is included in cisplatin-containing regimens. Objective responses were seen in 17 of 27 evaluable patients (63%) with cisplatin/vindesine/mitomycin C.[47] In 31 previously untreated patients with metastatic disease who received vindesine/cisplatin, an overall response rate of 52% was seen (complete response 16% and partial response 36%).[48] The median durations of complete and partial remissions were 64 and 44 months, respectively.

Vindesine is more effective when used in combination regimens. It has been used as part of two induction regimens investigated in sequential randomized trials at the Institute Curie[49] (Table 5). Two hundred and eight patients with advanced T3 and T4 head and neck cancer were randomized to local treatment with or without neoadjuvant chemotherapy. Two chemotherapy regimens were used: cisplatin/bleomycin/vindesine/mitomycin C/methylprednisolone for two cycles followed by local treatment or cisplatin/5-fluorouracil/vindesine for a total of three cycles followed by local treatment. Toxicity of the chemotherapy regimens was tolerable with no modification of local therapy. Both the number of complete and partial responses were higher for the second treatment group (complete response rate 22 versus 10%; partial response rate 48 versus 40%). The difference in response rate may be explained by the additional cycle of chemotherapy. Although there was no significant survival advantage or improvement in local control with neoadjuvant chemotherapy, a significant decrease in distant metastases was seen when the data for the two groups were combined.

Merlano *et al.* developed a vinca-containing neoadjuvant regimen.[50] Patients were randomized to either four courses of chemotherapy followed within 3 weeks by radiotherapy or four courses of chemotherapy with radiotherapy after the second, third and fourth chemotherapy courses. The chemotherapy regimen was the same in both arms of the study (vinblastine/bleomycin/methotrexate and leucovorin rescue). The complete response rate was seven of 48 and 19 of 57 in the sequential and alternating arms of the study, respectively ($p < 0.03$). The corresponding 4-year disease-free and overall survivals were 4 and 12% ($p < 0.02$) and 10 and 22% ($p < 0.02$), respectively. The authors concluded that the alternating regimen offered better local control and longer survival.

Preservation of organ function

In patients with operable, locally advanced squamous cell carcinoma, surgery results in 5-year survival in less than 50% of patients and radical surgical procedures affect the future quality of life. The strategy of organ preservation consists of the administration of induction chemotherapy (two to three cycles) with partial or complete responders having radiotherapy as a local treatment, resulting in organ preservation. Non-responding patients complete the treatment with radical surgery.

Various phase II trials had the goal of larynx preservation, some used cisplatin-based chemotherapy which included vinblastine.[51,52] The conclusion was that larynx preservation is feasible; almost one-third of the patients being free of disease, having long survival and their organ function preserved. This observation was confirmed by the only two site-specific randomized trials published up to now; one carried out by the Veterans' Affairs Laryngeal Cancer Study group[53] and the other by the EORTC Head and Neck Cooperative Group.[54] The former study showed that laryngeal preservation could be achieved without jeopardizing survival with the use of induction chemotherapy followed by radiotherapy. The EORTC trial attempted organ preservation (avoiding laryngopharyngectomy) for tumors arising in the hypopharynx. With a median follow-up of 51 months, the median survival for patients assigned to receive induction chemotherapy and surgery was 44 and 25 months, respectively, the same as for local control and with fewer distant relapses in the chemotherapy arm. These two trials are central in bringing about a change in the standards of care, i.e. avoiding surgery in operable and responding patients treated with neoadjuvant chemotherapy.

An important clinical outcome for patients with head and neck cancer is quality of life. Surgery may be extensive and the consequences of some surgical procedures, e.g. laryngectomy, affect breathing, speech, chewing or swallowing, and are associated with marked reductions in quality of life. Neoadjuvant chemotherapy may enable partial laryngectomy thus preserving laryngeal function without reducing survival.

Conclusions

The optimal form of treatment for patients with inoperable stage III and IV NSCLC remains controversial. However, there is a general consensus that patients should be encouraged to participate in clinical trials evaluating chemotherapy as their initial treatment programme. A common thread in all the chemotherapy regimens tested to date is high-dose cisplatin. These regimens usually produce response rates in excess of 50%. Resection rates with cisplatin-based chemotherapy usually exceed 50% and median survival is in the range 11–34 months (mode 20 months). The addition of concomitant or sequential radiotherapy is generally without additional effect.

Table 5. Randomized trial of neoadjuvant chemotherapy versus locoregional treament alone in head and neck cancer

Reference	No. of patients	Chemotherapy regimen	Results
66	96	MTX	No difference in survival.
67	638	MTX	No difference in survival.
68	23	VCR+MTX	Marginal increase in survival with chemotherapy.
69	86	VCR+MTX+5-FU+6MP+CPM	Advantage in survival for control arm.
70	83	CPM+BLM+MTX+5-FU	Advantage in survival for control arm.
71	443	DDP+BLM+MTX	No difference in survival.
72	60	DDP+5-FU	Advantage in survival for control arm.
73	158	DDP+VCR+MTX+BLM	No difference in survival.
74	75	DDP+5-FU	No difference in survival.
53	332	DDP+5-FU	No difference in survival. More local recurrences and fewer distant metastases in the chemotherapy arm.
75	116	BLM+MTX+5-FU+DDP	No difference in survival.
76	60	VLB+MTC+DDP+BLM	No difference in survival.
49	100	DDP+BLM+VDS+MTC+DDP +5-FU+VDS	No difference in survival. Significant reduction in distant metastases with chemotherapy.
74	75	DDP+5-FU	No difference in survival.

MTX, methotrexate; CPM, cyclophosphamide; 6MP, 6-mercaptopurine; VCR, vincristine; BLM, bleomycin; 5-FU, 5-fluorouracil; DDP, cisplatin; VDS, vindesine; MTC, mitomycin; VLB, vinblastine.

The goals of neoadjuvant therapy for NSCLC should focus towards improving chemotherapy regimens to increase response rate. Currently, at least 25% of patients fail to respond to induction chemotherapy and most of those who do not respond initially and undergo resection, subsequently relapse. Approximately 60% of all recurrences occur in the first 2 years of treatment. Two-thirds of the recurrences are systemic. New regimens are urgently needed to reduce this incidence.

Experience indicates that patients who attain complete responses to neoadjuvant therapy have the highest resection and survival rates. This emphasizes the need to identify new chemotherapy regimens that will raise the complete response rates above the 20% level that is currently achievable and, therefore, complete response rate should be the primary outcome variable in clinical trials.

The impact of neoadjuvant chemotherapy on survival is yet to be confirmed. Although the reported studies suggest that neoadjuvant chemotherapy improves survival, the wide variation in study design and chemotherapy regimens makes assessment difficult. Further well-designed randomized clinical trials are needed. The toxicity of aggressive chemotherapy is also of concern. The study by Fischer *et al.* used G-CSF to limit the duration and severity of neutropenia. Mehta *et al.* administered a combination of cisplatin and vinblastine with radiotherapy as neoadjuvant therapy to patients with stage III NSCLC. The regimen was supported with amifostine, a broad spectrum cytoprotective agent. A response rate of 61% was achieved. During chemotherapy, the incidence of WHO grade 3 or 4 neutropenia was 81% but there were no deaths from infection. There was no WHO grade 3 or 4 esophagitis or myelosuppression during radiotherapy.[55]

Although combinations of cisplatin and vindesine have been shown to produce good response rates when used post-operatively or as palliative therapy, these regimens have not adequately been evaluated as neoadjuvant therapy. Randomized controlled clinical trials should be specifically designed to evaluate vindesine in this role.

Patient selection undoubtedly plays a major role in the outcome of aggressively managed locoregional NSCLC. Although the superiority of the neoadjuvant approach over surgery alone has been proven through controlled trials, the optimization of treatment is now necessary. Comparison with chemoradiotherapy is important and the use of surgery in responding patients should be questioned, since radiotherapy could (and does) control locoregional disease responsive to chemotherapy.

In contrast with the results in NSCLC, the use of neoadjuvant chemotherapy in head and neck cancer is less conclusive, and randomized studies failed to demonstrate a survival benefit except when stage and site of disease were uniform in the eligibility criteria.[53,54] Other treatment approaches are needed to improve the poor prognosis of patients with advanced disease, e.g. concomitant chemoradiotherapy or alternating chemotherapy and radiotherapy. However, neoadjuvant chemotherapy may help preserve organ function and thus improve quality of life of patients. Further studies are needed to expand and determine the limits of this approach with current therapeutic armamentarium.

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