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Review paper

Chemotherapy versus palliative care in non-small cell lung cancer

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Non-small cell lung cancer (NSCLC) is the world's leading cause of cancer death and about 75% of all patients have advanced disease incurable with localized treatments (surgery and radiotherapy) alone. The aims of therapy in these are palliation of symptoms and extension of life. A substantial body of evidence has emerged in the last 15 years which shows that cisplatin-based combination chemotherapy prolongs life in advanced NSCLC. This evidence, which was well summarized in a major meta-analysis published in 1995, indicated that the degree of impact on survival is modest. Hence the balance between survival benefit and treatment-related toxicity is crucial in all considerations of chemotherapy in this disease. More recently this balance has been altered by considerable progress in the reduction of treatment-related toxicity and by documentation of lung cancer symptom palliation by effective chemotherapy. In 1999 a randomized trial of mitomycin, ifosfamide and cisplating versus palliative care in 351 patients demonstrated a significant survival advantage for those receiving chemotherapy, which did not compromise their quality of life. This review looks forward to further progress employing newer agents both as first- and second-line chemotherapy in advanced NSCLC. [© 2000 Lippincott Williams & Wilkins.]

Key words: Chemotherapy, non-small cell lung cancer, palliative care.

Introduction

Carcinoma of the bronchus is the commonest tumor in the Western world, with approximately half a million new cases diagnosed annually.[1] In the US 178 000 people are diagnosed and about 160 000 die each year of lung cancer. In the UK death rates are comparable, whilst those of Eastern Europe and Russia are even higher, making it the leading cause of cancer-related mortality.[2]

Approximately 80% of tumors are histologically non-small cell lung cancer (NSCLC), i.e. either squamous, large cell or adenocarcinoma, and have a 5-year survival of only 12%.[3,4] Although surgical resection is potentially curative and is the treatment of choice, the criteria for operability are met in only about 20% of cases. Of the remainder, a small proportion with localized, unresectable disease may achieve long-term disease-free survival with radical radiotherapy (RT), more commonly nowadays following chemotherapy (CT), but the majority with advanced disease are treated with palliative intent. Standard palliative treatment includes analgesics, antibiotics, corticosteroids, RT and oxygen.

Palliative CT, defined as treatment in circumstances where the impact of intervention is insufficient to result in major survival advantage, but improves tumor-related symptoms, is not a new concept.[5] Indeed the first studies of CT in lung cancer, by Karnowsky in 1948, reported symptom relief in lung cancer patients, including some with NSCLC.[6] Research efforts since then have focused on the aim of extending life and concerns about side effects have diverted attention away from the palliative potential of CT. Recent progress in CT (e.g. new drug and analog development) and supportive care (SC) (e.g. effective anti-emetics) has substantially reduced the toxicity of CT and required recalculation of the risk/benefit equation.

Furthermore, patients may be more prepared to accept some toxicity for effective palliation, than for modest extension of life. In a recent American study, 81 patients with advanced NSCLC who had been previously treated with cisplatin-based chemotherapy were asked to indicate the minimal survival benefit required to accept the toxic effects of CT. Interestingly 68% chose CT for a significant

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reduction in symptoms even if there was no prolongation of life, but only 22% would accept chemotherapy over SC for a survival benefit of 3 months. The median survival threshold for accepting CT was 4.5 months for mild toxicity and 9 months for severe toxicity.[7]

Review of meta-analyses

Despite approximately 50 randomized trials over the past 30 years examining the efficacy of CT in NSCLC, its role remained uncertain primarily because these trials were too small to detect moderate treatment effects reliably.

A meta-analysis of seven published trials of CT versus SC in 706 patients with non-resectable NSCLC was therefore undertaken in 1993. The endpoints were the number of deaths at 3, 6, 9, 12 and 18 months. A p value of 0.01 was taken to be statistically significant. The meta-analysis revealed that mortality in patients with advanced NSCLC was significantly reduced during the first 6 months following CT, and that although not significant at 9 and 12 months there was no evidence to suggest a decreasing benefit with time.[8]

A larger meta-analysis, using updated individual patient data on 9387 randomized cases from 52 available trials (published and unpublished), was conducted in 1995 by the Non-small Cell Lung Cancer Collaborative Group in an attempt to evaluate the effects of cytotoxic therapy on survival. They investigated the effect of CT in four main treatment settings: early disease (surgery versus surgery+CT; surgery+RT versus surgery+RT+CT), locally advanced disease (radical RT versus radical RT+CT) and advanced disease (SC versus SC+CT). The results for cisplatin-containing regimens favored CT in all groups, and attained statistical significance when combined with radical RT and SC. The absolute survival benefit for radical RT+CT was 4% at 2 years. The absolute benefit at 1 year for SC+CT was 10%.

This meta-analysis provided the most reliable estimate of the average effect of CT in NSCLC of varying stages and suggested that cisplatin-based regimens have a valid role in the treatment of this disease. However, no determination of other essential drugs for improved survival could be made due to the heterogeneceity of these trials.[9] Large randomized trials are required to overcome the problems of meta-analysis, and provide information on the choice of regimens, associated toxicity and quality of life (QL) outcomes.

Chemotherapeutic options for inoperable NSCLC

Initial interest in CT for NSCLC began in the 1980s when several cisplatin-based regimens demonstrated objective responses in up to 50% of cases.[10] A meta-analysis of 6247 cases revealed that the most active agents, particularly when used in combination, were cisplatin, vindesine, vinblastine, mitomycin C and ifosfamide.[11] However, the clinical value of such intervention could not be determined by these studies.

MIC (mitomycin C, ifosfamide and cisplatin)

A phase II trial conducted in 1988 in Birmingham reported a high objective response rate, good side-effect profile and improved performance status in responding patients with NSCLC with MIC.[12] Subsequent randomized trials in all stages of disease have demonstrated the efficacy of MIC.[13–16] MIC CT has objective response rates of 54% in unresectable, localized NSCLC and 32% in extensive disease, which are comparable with newer combinations such as paclitaxel/carboplatin,[17] gemcitabine/cisplatin[18] and vinorelbine/cisplatin.[19]

Data from two parallel phase III trials with over 800 patients demonstrated the effects of MIC CT on survival and QL, and was published in 1999.[15] The trial compared the effects of MIC CT plus standard treatment (ST) with ST alone in 820 randomized patients with unresectable NSCLC, on survival and, in a cohort study, QL. Standard treatment in the UK consisted of palliative care (PC) for patients with advanced disease (MIC 2) and RT for those with unresectable, locally advanced disease (MIC 1).

The results for MIC 1 demonstrated a trend in favor of CT and improved survival, which was not statistically significant. The median survival time was 11.7 months (CT + RT) versus 9.7 months (RT alone), p=0.14.[15]

In advanced disease MIC 2 demonstrated a statistically significant prolongation of life with CT.[15] The median survival time was 6.7 months (CT+PC) compared with 4.8 months (PC alone), p=0.03.[15] This randomized trial also assessed QL in 134 patients for 6 weeks from the start of the CT using a questionnaire based on the European Organization for Research and Treatment of Cancer (EORTC) QL questionnaire and concluded that MIC CT prolonged survival without compromising QL.[15] Smaller trials have also concluded that cisplatin-based CT significantly improves survival in advanced NSCLC.[20,21]

MVP (mitomycin C, vinblastine and cisplatin)

A study of 120 patients with advanced stage (stage IIIB and IV) NSCLC treated with 3 weekly MVP demonstrated an objective response in 32% of patients. Patients with locally advanced disease had a significantly better response rate (52%) than those with stage IV disease (25%, $p<0.01$). Relief of tumor-related symptoms was achieved in 69% of patients; in 61% after the first course and in 96% after the second course in responding patients. Median survival was 5 months. The schedule was well tolerated, 19% of patients developed WHO grade 3/4 nausea and vomiting, only 3% developed significant alopecia and other toxicities were minimal.[22]

Gemcitabine ± cisplatin

Gemcitabine, a nucleoside analog, acts as a competitive substrate for incorporation into DNA and leads to chain termination. Four phase II studies of single-agent gemcitabine observed response rates of between 20 and 26%, with median survival of 7–10.5 months.[23–26] Furthermore, there were improvements in tumor-related symptoms, performance status and weight. Gemcitabine was well tolerated with a low incidence of myelosuppression, nausea, vomiting and alopecia.

Preclinical studies have indicated that gemcitabine has the potential to inhibit the repair process of cisplatin-induced DNA damage. Since gemcitabine and cisplatin have different toxicity profiles, a number of phase II trials have been conducted to assess the efficacy of this combination.

A trial of 53 patients with advanced disease using initial weekly phase-specific gemcitabine followed by cycle-specific cisplatin monthly demonstrated an overall response rate of 52%. The median survival was 13 months and the 1-year survival rate was 61%. Toxicity was generally low, and consisted primarily of mild oral toxicity, nausea, vomiting and alopecia; WHO grade 3 and 4 neutropenia occurred in 38.8 and 19%, respectively, and grade 4 myelosuppression in 7.7%.[27]

Vinorelbine ± cisplatin

Vinorelbine is a new semi-synthetic vinca alkaloid with activity in NSCLC. In a multi-center trial it has been compared with cisplatin plus vindesine and with cisplatin plus vinorelbine. Six hundred and twelve patients with advanced NSCLC from 45 different centers were randomized to one of the above regimens. An objective response rate of 30% was observed in the vinorelbine and cisplatin arm compared to 19% in the vindesine plus cisplatin group and 14% in the vinorelbine only arm with median survivals of 40, 32 and 31 weeks, respectively. Furthermore, although the vinorelbine plus cisplatin arm had significantly higher rates of neutropenia there was less neurotoxicity than with vindesine and cisplatin. This trial suggests that vinorelbine plus cisplatin is an active and well-tolerated regimen in advanced NSCLC, and that vinorelbine alone is a valid alternative for patients who are unable to receive cisplatin-based regimens.[28]

The efficacy of vinorelbine in the palliation of metastatic NSCLC has been further confirmed by a recent study which randomized 191 elderly patients (70 years of age or older) with advanced disease to receive either single-agent vinorelbine or best SC. QL was evaluated using the EORTC QL questionnaire. Vinorelbine-treated patients scored better than controls on QL functioning scales, had fewer lung cancer-related symptoms but worse treatment related toxicity. There was a statistically significant survival advantage for patients receiving vinorelbine (two sided p=0.03); median survival was increased from 21 to 28 weeks in this group.[29]

Taxanes

A British phase III trial randomized 157 patients with advanced NSCLC to receive either paclitaxel (200 mg/m^2) or best SC. Median survival was significantly longer in the paclitaxel group than in the best SC arm (6.8 versus 4.8 months, p=0.037). QL was not adversely affected by paclitaxel CT and in a subgroup of patients there was evidence of significant improvement in functional activity. This study confirms that paclitaxel used first line is one of the more active agents in the treatment of advanced NSCLC.[30]A recent multicenter phase III study compared the use of docetaxel in 204 patients with metastatic or locally advanced NSCLC, who had progressed after one or more platinum-based CT, with best SC. The first 100 patients randomized received a docetaxel dose of 100 mg/m^2 by 1 h i.v. infusion on days 1 and 21. In subsequent patients (101–204) the drug was administered at a dose of 75 mg/m^2 by 1 h i.v. infusion on days 1 and 21, due to safety considerations with the higher dose. Patients continued in the study until there was evidence of progressive disease or unacceptable side effects. The median number of cycles administered was four. The best SC arm received no CT but were allowed palliative RT.

Despite previous CT, patients receiving docetaxel (75 mg/m^2) had a significantly longer median time to

progression than best SC (12 versus 7 weeks, p=0.004), a better 1-year survival (40 versus 16%, p=0.016) and a longer median survival (9 versus 5 months, p=0.016). Docetaxel (100 mg/m^2) also demonstrated better overall survival than best SC, with median survivals of 7 versus 5 months, respectively, and a significantly improved time to progression (9 versus 6 weeks, p=0.037).

Toxicity for docetaxel (75 mg/m^2) consisted primarily of grade 3/4 allergy (7% docetaxel versus 0% SC), diarrhea (2 versus 0%) and stomatitis (2 versus 0%). These side effects were expected and were offset by a marked reduction in tumor-related symptoms such as asthenia, pain, pulmonary and neurological symptoms. Infection occurred in 6% and was comparable in both groups. Toxicity was greater for the higher dose and there was not a significant improvement in palliation or survival compared to 75 mg/m^2. This trial, although not fully published, suggests a significant benefit for docetaxel (75 mg/m^2) when used as a second- or third-line agent in the palliative treatment of NSCLC.[31]

Conclusion

There is now overwhelming evidence to support the use of cisplatin-based CT in advanced NSCLC. Survival benefits, although incontrovertible, are modest and, if achieved at the expense of major toxicity, hard to justify. However, an increasing body of evidence suggests that toxicity can be negligible and is more than outweighed by relief of tumor-related symptoms. It also appears that patients are prepared to accept some toxicity in return for palliation.

The 1990s have seen the emergence of new drugs with clear activity in NSCLC. Data are accumulating to support the use of taxanes, gemcitabine and vinorelbine, both for survival and QL gains, in previously untreated advanced disease. Recent trial evidence suggests that docetaxel may have a role as second-line CT in patients previously treated with cisplatin-based combinations, again enhancing survival and QL. Therefore, so called 'best SC' may now be second best for many patients with advanced NSCLC.

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