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STAGE III A & B NON-SMALL CELL LUNG CANCER;
RATIONALE OF CONCOMITANT CHEMORADIOTHERAPY FOLLOWED BY CONSOLIDATION CHEMOTHERAPY AND PROPHYLACTIC CRANIAL IRRADIATION

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INTRODUCTION

Stage IIIA Non- Small Cell Lung Cancer (NSCLC) is characterized by the presence of ipsilateral mediastinal and / or sub carinal nodal involvement (N2) associated with a T1 or T2 primary lesion or a T3 lesion associated either with positive hilar nodes (N1) or with N2 nodal disease. Stage IIIB disease is characterized by scalene, supra-clavicular, contra lateral mediastinal, or contralateral hilar lymph node involvement (N3) associated with any T category or a T4 primary tumor associated with any N category1. Patients with stage IIIA disease can be stratified into those with bulky and nonbulky disease, based upon the presence of lymph nodes >2 cm in short-axis diameter, or groupings of multiple smaller lymph nodes[2]. Patients with bulky stage IIIA or those with stage IIIB disease are generally considered inoperable.

The combined modality therapy is the most common approach to treatment for these patients. It includes the administration of chemotherapy before radiotherapy or concomitant with radiotherapy or after radiotherapy as consolidation. Sequential chemotherapy followed by radiotherapy offers several theoretical advantages. Decreased tumor volume before radiotherapy leads to a better local control with subsequent radiotherapy. Chemotherapy before radiotherapy is better tolerated as compared to the administration with or

after radiotherapy and it provides an early treatment of micro metastatic disease.

Concurrent administration of chemotherapy and radiotherapy exploits the synergistic effect of chemotherapy and radiotherapy to enhance local tumor eradication and simultaneously treats the micro metastasis.

Amongst these two therapeutic options, concurrent chemo-radiotherapy using standard doses of platinum-based chemotherapy provides a survival benefit, and has emerged as the preferred approach despite the increase in treatment-related toxicity. With the concomitant systemic and loco regional treatment fewer patients now relapse locally and even distant relapses are also becoming less frequent except for the brain metastasis. And with the use of concurrent chemo-radiotherapy followed by consolidation chemotherapy brain metastases are likely to become the first site of relapse.

Therefore it is logical to consider that the Prophylactic Cranial Irradiation (PCI) may possibly prevent brain metastases and prolong survival in these patients.

SCIENTIFIC RATIONALE

Radiotherapy provides effective palliation for regionally advanced stage III disease, but it does not significantly improved survival in a majority of treated patients[3]. A number of studies have shown that radiotherapy alone achieves a median survival of 8-10 months only and a 5-year survival rate of 5-8 percent[4"12].

Many randomized trials have explored the possible benefit of adding systemic chemotherapy before definitive radiation in locally advanced non-small cell lung cancer. Cancer and Leukemia Group B trial 8433 included 155 patients who were randomly assigned to 60 Gy radiotherapy alone for 6 weeks, or radiotherapy preceded by two cycles of chemotherapy. The Five year survival probability was 2.8 folds greater in the chemo-radiotherapy group[6]. A subsequent Inter-group trial designed to confirm the findings of above trial revealed a different outcome. Two year survival results favored chemo-radiotherapy, but benefits disappeared at 3 years and at 5 years survival rates for chemo-radiotherapy and non-chemo-radiotherapy groups were similar[13]. Many other randomized trials have also failed to show significant benefit of sequential chemo-radiotherapy[14"15].

To date three meta-analyses have been performed to assess the value of adding chemotherapy to radiotherapy[15"18]. These indicate that sequential chemo-radiotherapy offers modest survival benefit but this seems to be restricted to the first two years following therapy and non-platinum regimens do not confer this benefit. In all these studies loco-regional failure remains a significant problem.

Benefits from sequential chemo-radiotherapy shall come from early control of distant metastases. Sequential chemo-radiotherapy also has the advantage that it avoids overlapping toxicities and it also ensures that both modalities are given in optimal doses. But these advantages do not translate in remarkable improvement of results, as the sites of major failures are not only the distant organs but also the sites of loco-regional disease.

The control of loco-regional disease can be improved with efforts to maximize local treatment by concomitant chemo-radiotherapy.

Concomitant chemo-radiotherapy provides an opportunity to control the loco regional and distant disease simultaneously. Many randomized trials directly compare concurrent chemo-radiotherapy with sequential chemotherapy and thoracic radiation 1[9"21.] One of these randomized trials shows a statistically significant advantage for concomitant

therapy while other trials only show a non-significant trend toward improved median survival.

A Japanese trial randomly assigned 320 patients with unresectable stage III patients to concomitant chemotherapy with cisplatin 80 mg / m^2 day 1 & 29, mitomycin 8 mg / m^2 day 1 and 29, and vindesine 93 mg / m^2 on day 1, 6, 29, 36 plus two courses of 28 Gy radiation separated by 10 days or same chemotherapy given before a continuous radiation of 56 Gy. Concurrent therapy achieved a significant increase in response rate, median survival and 5 year survival[19'22]. Median survival for concomitant, arm was 16.5 months Vs 13.3 months achieved in sequential arm (P=<.05). Three year survival was 22.3% with concurrent therapy compared to 14.7 with sequential therapy.

RTOG assigned patients to sequential cisplatin followed by radiotherapy, same chemotherapy concurrent with radiation and chemotherapy concurrent with hyper-fractionated radiation. There was non-significant trend towards improved survival in concurrent standard arm[20].

A French trial randomized patients into sequential chemotherapy with cisplatin 120 mg / m^2 day 1 & 29 plus vinorelbine 30 mg / m^2 weekly from day 1 -78 followed by 66 Gy thoracic radiotherapy with two Gy per fraction or concurrent chemo-radiotherapy with cisplatin 20 mg / m^2 and etoposide 50 mg / m^2 day 1-5 and day 29-33 with same dose of thoracic radiation. Concurrent therapy showed non-significant trend towards improved median survival and two-year survival21. In this trial, concurrent group also received two additional cycles of chemotherapy which can best be described as consolidation therapy.

Recently, Zemanova and colleagues have conducted a trial comparing sequential therapy with delayed concurrent therapy. Chemotherapy in each arm was identical, and included cisplatin 80 mg / m^2 day 1, with vinorelbine 25 mg/m^2 days 1,8,15 and with vinorelbine dose reduced to 12.5 mg/m^2 during cycle 2 and 3 on the concurrent arm. Treatment was repeated at 4 weeks interval. In concurrent arm, radiation was started on day 4 of cycle 2, and in sequential arm, radiation was started after completion of four cycles of chemotherapy. The overall response rate in the concurrent arm was 80.4 % vs. 46.8% in the sequential arm. Two year survival was 42% for concurrent approach Vs 15% for sequential approach. However patients in concurrent arm experienced more anaemia, neutropenia, nausea, vomiting and oesophagitis but there were no treatment related deaths[23].

A recently reported randomized phase II trial, Locally Advanced Multi-modality Protocol (LAMP), compared sequential chemotherapy followed by radiation to the induction first approach and to the concurrent first' approach and showed that the longest survival was achieved with concurrent first approach. Induction and consolidation therapy consisted of paclitaxel 200 mg/m^2 -and carboplatin AUC 6 every three weeks. The paclitaxel dose was reduced to 45 mg/m^2 and carboplatin was reduced to AUC 2 weekly during radiation therapy. The " total radiation dose in each arm was 63 Gy. Concurrent ^ chemo-radiation and additional consolidation therapy showed the best median survival of 16.1 months compared with the 11 months for induction therapy followed by concurrent chemo.-radiation and 12.5 months * for the sequential approach. It is of interest to note that concurrent first approach also yielded the highest incidence of grade III or more oesophagitis. However, there was no treatment related death. Results of this trial indicate the superiority of concurrent chemoradiotherapy followed by consolidation over other approaches[24].

Patients who achieve a complete response, partial response or stable disease on concurrent chemoradiotherapy may benefit from further

chemotherapy.
SWOG has conducted two important studies using cisplatin and etoposide in one and docetaxel in another as consolidation therapy after concurrent chemoradiotherapy with cisplatin, etoposide and radiotherapy[25].

A multi-centric phase II study of cisplatin 50 mg / m^2 on day 1, 8, 29 and 36 plus etoposide 50 mg / m^2 day 1-5 and day 29-33 were given along with once daily chest radiotherapy of 2 Gy to a total dose of 61 Gy. In this study consolidation was achieved by subsequent administration of cisplatin and etoposide combination chemotherapy. Three and five year survival rates were 17 and 15%. However toxicity was substantial with G4 neutropenia in 32% and G3 and G4 oesophagitis in 12 and 8 % respectively[25].

In the second study, SWOG 9504, docetaxel was used for consolidation therapy. Docetaxel is of particular value for inclusion into chemo-radiotherapy regimens due to its activity in both first and second line therapy in metastatic

NSCLC. In this study, 83 eligible patients with pathologically staged III B NSCLC received three cycles ot docetaxel, at 75 mg / m^2 on first cycle, escalating to 100 mg / m^2 in cycle 2 and 3. Consolidation docetaxel was given 4-6 weeks after completion of current chemo-radiation. A final analysis demonstrated a median survival of 26 months, two year survival of 54% and 3 year survival of 37%. Most common single site of distant metastasis was the brain and eight patients (21%) relapsed only in the brain[26].

Thus the systemic and loco regional treatment has become sufficiently intense to render the brain as the major site of failure. And with this present approach of concurrent chemo-radiotherapy and consolidation chemotherapy brain metastases are likely to become the first sites of relapse particularly when the newer and more effective agents are being incorporated in concurrent treatment setting.

Therefore it is logical to consider that the Prophylactic Cranial Irradiation may possibly prevent brain metastases and prolong survival in these patients, PCI has been well established in the treatment of small-cell lung cancer and a meta-analysis has shown that it significantly improves survival[27].

PCI has not been studied well in NSCLC patients. Only in a few randomized trials PCI has been added to thoracic irradiation in locally advanced NSCLC and there it has demonstrated reduced rate of development of brain metastases[2831]. In these trials the impact on survival could not be seen simply because the local and systemic treatments were not sufficiently successful in controlling the local disease and distant disease at sites other than brain.

With these considerations it seems appropriate to study the benefits of adding PCI to treatment with concurrent chemo-radiotherapy followed by docetaxel consolidation. Based on this rationale Cancer Research Group Pakistan is evaluating the use of cisplatin, etoposide, and concomitant thoracic radiotherapy followed by docetaxel consolidation and prophylactic cranial irradiation in bulky stage III A & stage III B non-small cell lung cancer with the objectives to document its impact on the metastases free survival and overall survival.

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