Multimodality treatment in locally advanced non-small cell lung cancer

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Prognosis in patients with locally advanced non-small cell lung cancer (NSCLC) is poor (five year survival rate of 5% [1]). Radiotherapy (RT), chemotherapy (CT) and surgery (S), as single modality therapeutic approaches are unable to eradicate locoregional disease and to control systemic microscopic disease. Concurrent chemoradiation (CTRT) is at present time deemed to be the standard of care for inoperable locally advanced NSCLC [2]. In randomized trials this modality treatment has increased median survival from fourteen months of sequential approach to 17 months [3–7].

Nowadays, new evidences underline the role of a mixed approach with concurrent radio-chemotherapy followed by consolidation chemotherapy [3, 8].

In SWOG 9504, mixed approach using concurrent radiochemotherapy followed by consolidation docetaxel showed a median survival of 26 months with a 3-year survival of 37%, better than the results of previous SWOG 9014 [7] where the concurrent approach was the only performed.

Using carboplatin-paclitaxel chemotherapy, the LAMP study [3] confirmed a better survival of consolidation chemotherapy (16.3 months) vs. induction chemotherapy (12.7 months), but pointed out two major problems in treating these kinds of patients: non-haematological toxicity registered during radiochemotherapy (28% of grade 3+ oesophageal toxicity), and subsequently, compliance to planned treatment (only 67% of patients completed the concurrent CTRT and among these 75% received the full chemotherapy dose).

Higher rates of non-haematological toxicity have reported in the CALGB 9431 [9], where in the concurrent radiochemotherapy grade 3+ toxicity ranged from 25 to 52% for oesophageal toxicity and 14–24% for the pulmonary one.

In the light of these results, toxicity, particularly non-hematological toxicity, remains a major obstacle in treating patients with radio-chemotherapy.

A better toxicity profile could be reasonably achieved reducing the irradiating volume.

Besides, several authors underlines that despite the high risk of nodal spread in lung cancer, the value of inclusion of ENI is not proven and very little is known about its effectiveness.[10–14].

The main arguments for omitting ENI are as follows: when routine broncoscopy is performed after radiotherapy in locally advanced NSCLC, <20% of patients are controlled at 1 year [15]; the incidence of nodal progression in untreated mediastinal nodes is <6% [10–13]; in a combined chemotherapy-radiotherapy strategy, if chemotherapy is effective as a systemic therapy, it is reasonably to hypothesize that it may also control occult microscopical nodal disease [14]; mediastinal areas located in the proximity of the PTV often receive sufficient radiation doses for the treatment of occult metastases [16].

An emerging role of concurrent radio-chemotherapy is in the neoadjuvant setting.

Recently, results of the Intergroup Phase III trial 0139 (RTOG 93–09) [17], have been presented at ASCO in 2005. 396 patients with mediastinoscopy-proven IIIAN2 NSCLC, were randomized to receive either induction radio-chemotherapy or radical radio-chemotherapy with cisplatin 50 mg/m² on days 1, 8, 29, 36 and etoposide 50 mg/m² on days 1–5 and 29–33 was concurrent with daily RT up to 45 Gy in surgery arm, or to 61 Gy in standard treatment arm. Information from 88.8% of patients in surgery arm who underwent to complete resection, showed lymph node clearance (pN0 disease) in 46% of patients. A statistically significant improved 3-year progression free survival has been reported among patients of multimodality treatment approach (29% vs. 19%), but not yet translated in a better survival maybe due to early follow-up and to pneumonectomies. In fact, the survival in the subgroup of patients who received after concurrent chemoradiation a lobectomy have shown a better median survival (34 months versus 22 months) and five year overall survival (36% versus 18%).

Moreover interesting results have been recorded in patients who, after the induction treatment and at time of surgery, achieved a complete lymphnode clereace (i.e. absence of nodal involvement in pathology specimens). In this subset of patients the median survival was 34 months with a five year overall survival of 46%.

Other trials have underlined the importance of pathological response after any inductive treatment either in terms of nodal clearance [18] or referring to pathological downstaging [19–21], thus to consider the absence of tumor in mediadiastinal nodes as a surrogate end-point of survival.

Among these, the Journal of Clinical Oncology published in 1995 the final results of SWOG 88–05 [19], where a neoadjuvant radio-chemotherapy approach followed by surgery has been tested in NSCLC patients staged IIIA (N2) and IIIB. The objective response rate to induction was 59%, while resectability was 85% for the IIIA (N2) and 80% for the IIIB group. The
strongest predictor of long-term survival after thoracotomy was absence of tumor in the mediastinal nodes at surgery (median survivals, 30 vs. 10 months; 3-year survival rates, 44% vs. 18%; \( P = .0005 \)).

In another study Choi et al. [20] tested the potential impact on survival of improved tumor downstaging by preoperative radiation and concurrent chemotherapy in stage IIIA non-small-cell lung cancer. Pathologic examination of the surgical specimens showed a downward shift in tumor stage from stage IIIA (N2) to stage II (N1) in 33% of patients, to stage I (N0) in 24% (10 of 42), and to stage 0 (TONO) in 9.5%, for a total of 67% downstaged tumors. The degree of tumor downstaging was also translated into a survival benefit: 5-year survival rates from the time of surgery were 79%, 42%, and 18% for postoperative tumor stages 0 and I, II, and III, respectively (\( P = 0.04 \)).

In our experience 202 patients between February 1992 and October 2005 with locally advanced non-small cell lung cancer (IIIA(N2) or IIIB(T4)) have been treated with concurrent radiotherapy and chemotherapy. In every case the radiotherapy was administered only to visible neoplasia, thus excluding the elective nodal irradiation, with a total dose of 50.4 GY and daily dose of 1.8 GY. Concurrent chemotherapy was: Carboplatin (CBCDA) or Cisplatin and 5-FU (till February 2000), Gemcitabine (till June 2003) and Cisplatin plus Gemcitabine.

The results in terms of clinical response rate, surgical resection and pathological downstaging are shown in Table 1.

An Italian trial is actually ongoing to confirm the encouraging results of induction chemoradiation with Cisplatin and Gemcitabine.

### references