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NEO-ADJUVANT CHEMOTHERAPY IN EARLY STAGE DISEASE

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Survival in NSCLC remains poor also in early disease stages: the 5-year survival rate of patients who undergo complete surgical resection is only 40 to 50% and even in stage IA after complete resection, one third of the patients will relapse and die of their disease within 5 years. The relapse pattern is quite similar in all stages of the disease and all histological subtypes of NSCLC with intrathoracic relapses occurring in one third and distant relapses in 2/3 of the patients. The role of chemotherapy as adjuvant treatment was highly controversial for many years until the NSCLC meta-analysis, published in 1995, suggested a small benefit from platinum-based chemotherapy when associated to surgery with a reduction in mortality rate. A series of randomised clinical trials, almost all cisplatin-based were conducted in the last decade, but the expectation for large positive results from those trials is quite unrealistic.

In stage IIIA with N2 involvement the neo-adjuvant approach has been successfully tested in more than 25 phase II trials and two small randomised phase III trials, both terminated early on the basis of interim analyses, suggesting a twofold increase in overall survival time in comparison to that observed with surgery or radiation therapy alone.

The gemcitabine-cisplatin regimen was proven to be effective in unresectable locally advanced and metastatic NSCLC and, consequently it is a logical step forward to investigate the activity of this new combination in stage III NSCLC. Results of five phase II trials have been recently published reporting, in a mixed study population (IIIA and IIIB), an average response rate > 60% and a reasonable toxicity profile mainly when a three-week schedule of Gemcitabine was used. A phase III French study compared the administration of 2 courses of Mitomycin C, Ifosfamide and Cisplatin followed by surgery (n=187) compared to surgery alone (n=180) in resectable stage I (with the exclusion of T1N0 lesions), II and IIIA. A survival advantage, potentially delayed for high perioperative toxicity, was observed in the combined arm. Median survival time favored the combined approach (36 months versus 26 months, p=0.11, log-rank test). After 150 days the effect of perioperative chemotherapy on survival was significantly favorable (relative risk = 0.71, p=0.03). A quantitative interaction between N factor and treatment was also noted, with benefit from perioperative chemotherapy confined to N0-1 patients (p=0.008). Disease-free survival was significantly longer in the perioperative chemotherapy arm (p=0.02) with similar interaction with N0-1 patients (p=0.002). Perioperative chemotherapy induced a pathologic complete response in 19 patients (11%) and a pathologic partial response in 95 patients (53%) for an overall response rate of 64%.

At the same time a phase II trial was performed in USA and assessed the feasibility – in terms of response rate and toxicity, resectability rate, pCR rate and surgical mortality rate – of two courses of Paclitaxel 225 mg/m^2/3 hour infusion and Carboplatin AUC=6 given every 21 days followed by surgery in 94 patients with stage IB, II and selected IIIA NSCLC. Completely resected patients received three additional courses of Paclitaxel-Carboplatin after surgery. Ninety-two patients completed perioperative chemotherapy and major responses occurred in 59% of the enrolled patients. Of the 92 patients potentially eligible for surgery 80 (93%) were explored and 70 (82%) were completely resected. No increased or unexpected toxicity or surgical morbility have been observed. Based on the results of this feasibility study a randomized intergroup trial comparing three cycles of induction Paclitaxel-Carboplatin and surgery to surgery alone in early stage NSCLC have been already initiated in the USA and more than 200 patients have been already randomized. In Italy using a nearly identical study design a randomised clinical trial called ChEST (Chemotherapy for Early Stages Trial) of surgery alone or surgery plus preoperative gemcitabine-cisplatin in early clinical stages (T2-3N0,T1-2N1, T3N1) NSCLC has been launched in June 2000.

As primary end point of the study, ChEST will assess whether preoperative chemotherapy improves compared to surgery alone secondary end-points include overall survival and patterns of relapse, operative mortality and surgery-related morbilities, response rates and chemotherapy-related toxicities.

The sample size calculation is based on data of previous adjuvant chemotherapy in completely resected NSCLC (ALPI trial) in which the progression free survival at 3 years is expected to range from 45% to 55%, mainly depending by the distribution of the disease stage.

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Estimated efficacy of pre-operative chemotherapy might be in the range of 20%-25% reduction of event rate. This assumption is mainly based on NSCLC overview which demonstrate a 13% mortality reduction in the adjuvant setting, but a 27% mortality reduction in advanced disease, where compliance to treatment is usually higher. Estimate of sample size is based on these further following assumptions: duration of accrual of three years; minimum follow-up of further three years; a error equal to 0.05 (two sides) and b error of 0.20 using the log-rank test. Based on these assumptions the required number of events is about 390, corresponding to a number of patients ranging from 600 to 700.