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Induction therapy of loco-regional non-small-cell lung cancer with reliable response and low toxicity (low dose radiotherapy sensitizes tumor to subsequent chemotherapy?)

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ABSTRACT

Introduction: For the induction therapy of non-small-cell lung cancer, we need to look for a regimen which produces a reliable high response rate with a low treatment related morbidity and mortality.
Methods: Patients in clinical stages IB, IIA and B, IIIA and B received a course of therapy with 20 Gy of radiation in 2 weeks. This was followed by two courses of chemotherapy consisting of paclitaxel 180 mg/m^2, cisplatin 45 mg/m^2, and ifosfamide 1000 mg/m^2. Two to 3 weeks after chemotherapy, the patients were re-evaluated and, if suitable, underwent surgical therapy.
Results: A total of 35 patients were entered into the study. The overall response rate was 82.86% (95% confidence interval, 66.35–94.5%). Complete response (CR) was 20% (95% confidence interval, 8.44–36.94%). Twenty-five patients had surgical resection. Subsequently 18 patients received completion radiotherapy of additional 45 Gy. The median follow up is 30 months. In 12 patients with stages IB, IIA and B, the median survival was 61 months, and 5-year survival was 55%. In 23 patients with stages IIIA and B, the median survival was 26 months, and 5-year survival was 9.5%. There was 1 patient with Grade 4 and 13 patients with Grade 3 leukopenia, and half of them received granulocyte colony stimulating factor. By the completion radiotherapy, 6 out of 18 patients had less than Grade 2 esophagitis. Five patients had Grade 2 radiation pneumonitis and one Grade 5 (one mortality). There was no postoperative death. The survival results were comparable to those reported recently by others, however the regimen produced a high response rate with low treatment related morbidity/mortality.
Conclusion: It is a suitable regimen for induction therapy to include earlier stage resectable non-small-cell lung cancers.

1. Introduction

Complete surgical resection has been the mainstay of curative non-small-cell lung cancer (NSCLC) treatment [1–3]. However, numerous randomized controlled trials have now shown the combination of chemotherapy and surgery to be superior to surgery alone in local-regional NSCLC [4]. That this statement applies to both induction and adjuvant chemotherapy treatments shows the robustness of the result, even if the resulting improvement in survival is fairly modest. Since patients afflicted with lung cancer typically tolerate induction chemotherapy better than adjuvant treatment, considerable investigative attention has been devoted to identifying an optimal induction regimen. Most investigations have focused on platinum-based combinations of chemotherapeutic agents, with or without radiotherapy. When radiotherapy is added to the induction treatment it may be given concurrently or sequentially (chemotherapy and then radiotherapy). Treatment morbidity, however, is a major concern with these induction strategies. We have adopted a different approach to the sequencing of induction therapy: low dose radiotherapy, followed by chemotherapy and then surgery. This particular treatment modality was developed by us following an observation of unexpected good therapeutic results on a patient with stage IIIB lung cancer. In this report we present our early results, and argue that this treatment strategy is well tolerated, yields reliable response rate, and survival results broadly comparable to more traditional combined modality protocols.

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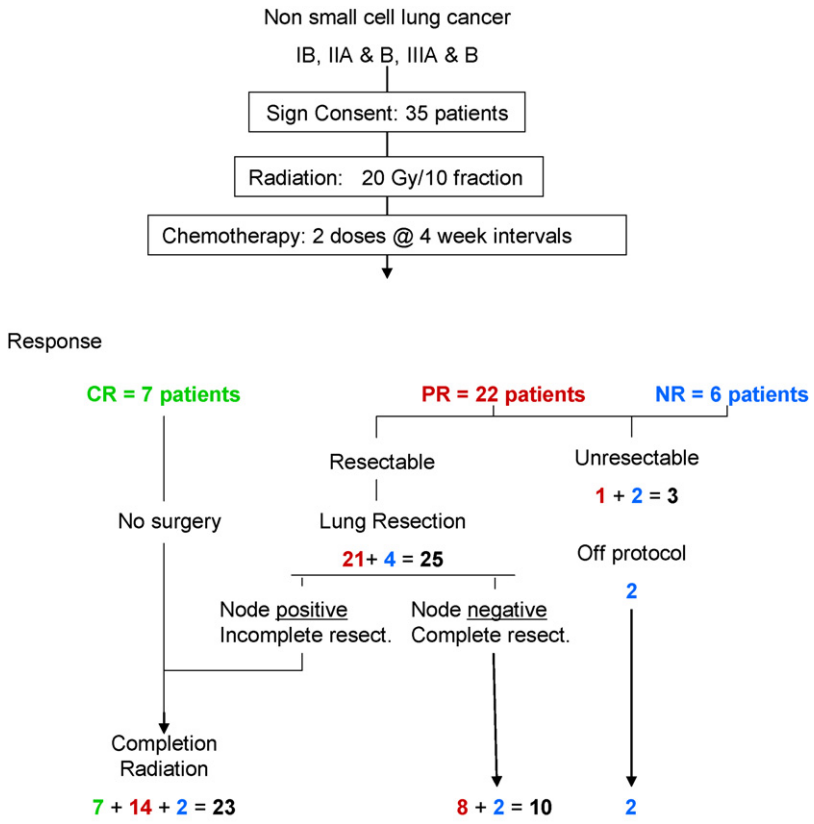

Fig. 1. Flow diagram of prospective Phase II study of induction radiotherapy followed by surgical resection for loco-regional non-small-lung cancer.

2. Patients and methods

A prospective phase II study of induction radio-chemotherapy followed by surgical resection, for local and regional NSCLC, was begun in 2000 (Fig. 1). Eligibility criteria included biopsy-proven NSCLC, clinical stages IB, IIA, IIB, IIIA, and IIIB disease, Eastern Cooperative Oncology Group (ECOG) performance 0 and 1, no prior chemotherapy or radiotherapy, no concurrent malignancy, and no past history of lung cancer. The protocol was approved by the IRB and the informed consent was obtained from all patients. Staging investigations included computed tomography (CT) scan of the chest and upper abdomen, positron emission tomography (PET) scan, and/or mediastinoscopy. Induction therapy consisted of a brief course of radiotherapy 20 Gy in 2 weeks to the primary lung cancer and to the mediastinum. This was followed by two courses of chemotherapy at 4-week interval. The thoracic radiotherapy was planned out for each patient using 3D conformal CT-based simulation. Gross tumor volume (GTV) was determined by abnormal findings (primary lung tumor + involved lymphnodes) based on diagnostic CT and PET scans. This was treated in 3D conformal fashion (typically four to six treatment fields) to a total dose of 20 Gy in 10 fractions. The chemotherapy consisted of paclitaxel 180 mg/m^2, 3 h intravenous infusion (IV), cisplatin 45 mg/m^2, 6 h IV, and ifosfamide with mesna 1000 mg/m^2, 6 h IV. Two to 4 weeks after completion of the therapy, the patients were re-evaluated by the physical examination, CBC, chemistries, pulmonary function tests, cardiac evaluation and CT scans of the chest and abdomen. Some stage III patients also had CT of the head, but PET scan was not used. If suitable, the patients underwent surgery in the next 2–4 weeks.

Following surgery, patients with pathological N_2 disease and with incomplete resection received further 45 Gy of radiation therapy in 25 fractions over 5 weeks Patients obtaining clinical complete response (CR) also received the same radiation therapy (instead of the surgery).

Upon completion of the treatment, the patients were followed every 4 months for 3 years, then every 6 months thereafter. At each visit, physical examination, CT scan of the chest and abdomen, CBC, and chemistries were done. When an evidence of recurrence or second primary lung cancer found, patients were treated off protocol. The clinical response evaluation was done according to the guidelines of the World Health Organization [5]. Response rates are expressed along with 95% confidence intervals (CI). Survival results are presented as Kaplan–Meier estimates.

3. Results

From February 2000 to February 2005, 35 patients, 18 males and 17 females, with ECOG performance status 0 and 1 were entered into this study. Ages ranged from 40 to 80 years; the median age being 65. Patients were diagnosed as follows: adenocarcinoma 16; squamous cell type 13; adeno-squamous cell carcinoma 1; atypical carcinoid tumor 1 (pretreatment biopsy was reported to be adenocarcinoma); and NSCLC 4. The clinical staging was as follows: IB 3 patients; IIA 1 patient; IIB 8 patients; IIIA 14 patients; and IIIB 9 patients.

Of 14 stage IIIA patients, 13 patients had mediastinal involvement. Eight of the 13 patients had bulky mediastinal adenopathy measuring 2–4 cm in size (obvious metastatic nodes): 6 had either PET scan or mediastinoscopy, and 2 had CT scan only. One patient had a vocal cord paralysis, and the remaining four patients had positive PET scan or mediastinoscopy. All nine patients with stage IIIB had either PET scan or node biopsy. All 12 patients with stage I and II diseases were staged noninvasively (6 had PET scan).