Int. J. Radiation Oncology Biol. Phys., Vol. 45, No. 5, pp. 1151–1156, 1999

0360-3016/99/$–see front matter

ELSEVIER

PII S0360-3016(99)00307-7

CLINICAL INVESTIGATION **Lung**

HYPERFRACTIONATED ACCELERATED RADIOTHERAPY (HART) FOR INOPERABLE, NONMETASTATIC NON-SMALL CELL LUNG CARCINOMA OF THE LUNG (NSCLC): RESULTS OF A PHASE II STUDY FOR PATIENTS INELIGIBLE FOR COMBINATION RADIOCHEMOTHERAPY

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Purpose: To evaluate a hyperfractionated and accelerated radiotherapy (HART) protocol in patients with inoperable non-small cell lung carcinoma (NSCLC) who were ineligible for combination radiochemotherapy studies.

Methods and Materials: From February 1989 through August 1994, 23 patients ineligible for available combined modality protocols in our institution were enrolled and treated with HART, consisting of 63 Gy given in 42 fractions of 1.5 Gy each, twice daily, with a minimum time interval of 6 h between fractions, 5 days a week, over an elapsed time of 4.2 weeks, or 29 days. There was no planned interruption.

Results: The 1-, 2-, and 3-year survival rates were 61%, 39%, and 19%, respectively, with a median survival of 16.8 months. At the time of analysis, 4 patients are alive and 19 have died, 16 from NSCLC and 3 from cardiac disease. Overall response rate was 48%, with 22% of patients achieving a complete response and 26% a partial response. Correlation between acute response rate and survival was poor. First site of relapse was local-regional in 8 patients (35%), distant in 6 patients (26%), and local-regional and distant in 4 (17%) patients. One patient had Grade IV and 2 had Grade III esophagitis. One patient presented with chronic Grade III lung toxicity. There were no treatment-related deaths.

Conclusion: In this group of 23 patients ineligible for radiochemotherapy, this HART regime was quite feasible and was followed by little toxicity. Results in this particularly poor prognosis NSCLC patient category should be compared to series with a similar patient profile; however, median survival is at least similar to that obtained in recent series of combination radiochemotherapy. © 1999 Elsevier Science Inc.

Non-small cell lung cancer, Radiotherapy, Accelerated radiotherapy.

INTRODUCTION

In spite of the many advances in surgery, radiotherapy, chemotherapy, or their combinations, locally advanced Stage IIIA and IIIB non-small cell lung cancer (NSCLC) remains a disease category with a poor overall prognosis, and the optimal treatment remains unknown (1). With conventional radiotherapy (RT) alone, both local and distant failure rates are high, and the expected median survival is generally between 9 and 12 months (2, 3). To improve the local control, surgery following induction chemotherapy, radiotherapy, or both can be attempted (4, 5); however, this approach is applicable only to the subgroup of patients with potentially resectable tumors. Dose-escalation via three-dimensional (3D) planning and conformal radiotherapy is an important development, and is currently being investigated (6–8). Combination chemotherapy and radiotherapy have been extensively studied with a large number of drug associations and radiochemotherapy schedules (9, 10). Meta-analyses have concluded that results favor combined cisplatin-based chemotherapy; however, the gain in terms of 3- and 5-year survival is quite modest (11, 12). Moreover, a substantial subset of patients cannot be treated with chemotherapy because of various medical or psychological reasons.

Unconventionally fractionated radiotherapy, mainly hyperfractionated accelerated radiotherapy (HART) (13–15) and continuous hyperfractionated accelerated radiotherapy (CHART) (16, 17) offer interesting alternatives in locally advanced NSCLC.

We report here our experience with a HART protocol in a Phase II study for patients with inoperable NSCLC who could not be enrolled in combination radiochemotherapy protocols.

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Accepted for publication 22 July 1999.

Table 1. Reasons for patient exclusion from combined radiochemotherapy GOTHA I and II studies

Condition	No. of patients
Severe heart disease	12
Severe chronic lung disease	6
Age > 70 years	1
Weight loss > 10% in 6 months	1
Two pulmonary tumors	1
Patient refused chemotherapy	3

PATIENTS AND METHODS

Eligibility and study parameters

Between February 1989 and August 1994, 23 patients were entered in this Phase II trial. Patients with pathologically or cytologically documented squamous cell carcinoma, adenocarcinoma, large cell, or undifferentiated NSCLC with either inoperable Stage IIIA or IIIB (with the exception of patients with pleural or pericardial effusion), or medically inoperable Stage I or II were considered to be eligible. This series of 23 consecutive patients represents a subgroup of all inoperable NSCLC seen in our department, who could not be enrolled in on-going trials of combined radiochemotherapy available at this time, namely the GOTHA I and II trials (18, 19). These priority protocols in our department consisted of different schemes of combination cisplatin-based chemotherapy, rapidly alternated with hyperfractionated-accelerated RT.

The reasons for ineligibility of these 23 patients from the combined modality trials are shown in Table 1, any of which representing exclusion criteria from GOTHA I and II. The majority of patients presented with chronic medical conditions, mainly heart and lung diseases, precluding the administration of aggressive radiochemotherapy schedules.

A review was made retrospectively on the histological or cytological material, which was available for 21 patients. The diagnosis of NSCLC was confirmed in all cases. Two patients with Stage I and 1 patient with Stage II disease, who were considered as medically inoperable, were included in the study, and the remaining 20 patients had surgically inoperable Stage III disease.

Thus, patients either with surgically unresectable or medically inoperable tumors were eligible for this Phase II trial, but those with previous radiotherapy, surgery, or previous chemotherapy were excluded. Other requirements for eligibility were a forced expiratory volume of 1.5 liters or more, and the absence of hematogenous metastases on work-up.

The pretreatment evaluation included AP and lateral chest X-ray, thoracic computed tomography (CT), and bronchoscopy in all patients. Twenty-two (96%) patients had bone scintigram and 19 (83%) had upper abdominal CT. Ten (44%) patients underwent brain CT or magnetic resonance imaging (MRI).

Treatment scheme

The radiotherapy scheme was adapted from GOTHA I and II, the major difference being that it did not include any interruption. (In GOTHA I and II, a 2-week split was mandatory for the administration of the second cycle of chemotherapy) (18, 19).

Thus, patients were treated with a HART without any planned interruption, consisting of 63 Gy delivered in 42 fractions of 1.5 Gy each, twice daily, with a minimum time interval of 6 h between fractions, 5 days a week. The scheduled overall duration of treatment was 29 days (4.2 weeks). A dose of 40.5 Gy was given to the first planning target volume, encompassing the primary tumor, draining ipsilateral hilar lymph nodes, mediastinum, thoracic inlet, and the supraclavicular fossae. This volume was treated with anterior-posterior parallel-opposed fields. An additional dose of 22.5 Gy was given to the second planning target volume, comprising only the primary tumor and grossly involved lymph nodes, to a total dose of 63 Gy. That volume was treated in 22 patients with oblique, parallel-opposed, off-the-cord reduced fields, and in 1 patient with lateral parallel-opposed fields. Megavoltage (6 and 18 MV), isocentric technique, and cerrobend blocking were required. For planning purposes, simulator and dosimetry with treatment planning computers were mandatory.

Evaluation of toxicity and response, patient follow-up

Study endpoints were acute toxicity, late normal tissue damage, tumor response, and survival. Acute toxicity, using WHO grading, was defined as toxicity occurring during or at the end of RT. Chronic toxicity was defined as toxicity occurring after 90 days following the start of RT, or when acute reactions persisted over 90 days, using the RTOG scale.

The assessment of tumor response was based on the comparison of the initial tumor measurements 4–8 weeks after completion of the radiotherapy. A complete response was defined as the total disappearance of the tumor on chest radiography and chest CT.

A partial response was considered as a 50% or more reduction of the sum of the products of the greatest perpendicular diameters of the tumor, whereas progression corresponded to a 25% or more increase of the sum of these diameters. No change was defined as less than 50% reduction or less than 25% progression of the tumor.

All patients were to be followed for the duration of their life, monthly during the first year, every three months in the second year, and yearly afterwards, and the date and site of first failure were registered. In case of failure, the choice of treatment was made on an individual basis.

Statistical methods

The overall survival (OS) was measured from the first day of treatment to death from any cause or to the date of last follow-up if the patient was alive. For the evaluation of progression-free survival (PFS), the date of first progression, or death from any cause or the date of last evaluation

Table 2. Patient characteristics in the HART study and in GOTHA I and II

	HART	GOTHA I & II
No. of patients	23	132
Median age (years)	63.8 (46–75)	55.5 (28–70)
Male/Female	22/1	7.3/1
Cell types		
Squamous cell	18 (78%)	66%
Adenocarcinoma	2 (9%)	22%
Large cell carcinoma	2 (9%)	14%
Non-small cell undifferentiated	1 (4%)	4%
Stage		
I	2 (9%)	0%
II	1 (4%)	0%
IIIa	5 (22%)	44%
IIIb	15 (65%)	56%
PS		
0	2 (9%)	36%
1	13 (56%)	52%
2	8 (35%)	12%

if the patient had no evidence of disease, was considered. The probability of survival was calculated according to the method of Kaplan-Meier (20) and the corresponding standard error by Greenwood formula (21). Cox regression analysis was used to test the simultaneous effect of age, performance status (0 vs. 1 vs. 2), and duration of treatment on the risk of death (22).

RESULTS

Patients

Twenty-three patients were accrued between February 1989 and August 1994; all have been included in the analysis. Table 2 summarizes the characteristics of the patients: the median age was 63.8 years; the male to female ratio was 22:1; the WHO performance status was 0 in 2 patients, 1 in 13, and 2 in 8 patients, respectively. Histologic types consisted of squamous cell carcinoma in 18, adenocarcinoma in 2, large-cell carcinoma in 2, and undifferentiated non-small cell carcinoma in 1 patient. Three patients had Stage I and II, 5 had Stage IIIA, and 15 had Stage IIIB disease.

Of these, 4 patients presented with a T2 tumor, 7 with a T3, and 12 with a T4 lesion. Ten patients had clinically and radiologically negative lymph nodes (NO). One patient underwent a blank thoracotomy before RT.

Table 2 also compares patients of the present study to those included in GOTHA I and II studies (19).

Feasibility and dose intensity

All patients were irradiated to the first planning target volume with a median doses of 40.5 Gy (range 26–43). One patient refused any further RT because of fatigue, and another decided to have a break after he had received 40.5 Gy, also because of fatigue, but resumed his RT 2 weeks afterward. Twenty-two of 23 patients (96%) were irradiated to the second planning target volume, with a median dose of 22.5 Gy (range 19.5–27). The median total dose was 63 Gy (range 40.5–66), and the median duration of treatment was 30 days (range 23–46), one day longer than scheduled (29 days).

Response, survival, and pattern of failure

The overall response rate at first control after 4-8 weeks was 48%, with 5 (22%) patients achieving a complete response and 6 (26%) patients showing a partial response. Eight (35%) patients had no change, no patient was in progression, and 4 were inevaluable.

The 1-, 2-, and 3-year survival rates were 61% (± 10), 39% (± 10), and 19% (± 8), respectively, with a median survival of 16.8 months.

Apparently, there was no correlation between the degree of response and survival: among the seven patients surviving 2 years or more, only one had a complete response, two a partial response, and four had no change in their tumor size. Conversely, of the five patients who were scored as having a complete response, four died within 2 years.

At the time of analysis, 16 (70%) patients were dead from their pulmonary carcinoma and three (13%) from other causes: two patients died of myocardial infarction and one of acute left cardiac insufficiency. Two (9%) patients were alive with disease and two (9%) were free of disease.

The median progression-free survival was 10.2 months. The events contributing to the progression-free survival were 5 deaths as first event and 16 progressions. There were no differences in overall survival and progression-free survival attributable to age, performance status, and duration of treatment when such factors were considered in the Cox regression analyses; however, the number of patients in each category was quite small.

Sites of first failure were as follows: 8 patients (35%) had local-regional failures, 4 (17%) distant failures, and 6 (26%) both local-regional and distant failures. Of the 14 patients with a local failure component, 10 had radiological tumor persistence at the time of first evaluation after treatment.

Toxicity

As seen in Table 3, acute toxicity was quite moderate. One patient had Grade IV acute esophagitis, requiring nasogastric tube feeding, and two patients had acute Grade III esophagitis; all of these eventually resolved. One patient had chronic Grade III dyspnea, the only significant chronic toxicity of the study. When considering either AP-PA field size or oblique boost field size, there was no significant influence on the occurrence of Grade III–IV esophageal or lung toxicity.

DISCUSSION

For decades, especially the past 20 years, many efforts have been made to improve the results of radiotherapy for inoperable and locally advanced NSCLC. These have comprised various combinations of chemotherapy and radiotherapy (9, 10).

Table 3. Treatment scheme and results of the HART study compared to GOTHA I and II

	HART	GOTHA I & II
Study protocol	HART alone	Alternated chemotherapy and HART
Radiotherapy	63 Gy, 1.5 Gy b.i.d., no split	63 Gy, 1.5 Gy b.i.d., 15-day split after 30 Gy
Median RT treatment time (days)	29	46
Chemotherapy	None	GOTHA I: cisplatin, mitomycin, vindesin GOTHA II: cisplatin, vinblastine
Median survival (months)	16.8	13.6
1-, 2-, 3-year survival	61%, 39%, 19%	56%, 27%, 17%
Acute Grade III–IV mucositis	3/23* (13%)	18/132 (14%)
Late pulmonary toxicity	1/23† (4%)	8/132 (6%)

* Two patients had Grade III and one patient had Grade IV esophagitis.
† One patient had Grade III late pulmonary toxicity.

Several trials comparing radiotherapy alone to cisplatin-based chemotherapy associated with radiotherapy have shown that the combined modality was better; however, meta-analyses have indicated that the gain in 3- and 5-year survival was quite modest (11, 12). In addition, attempts were made to increase the intensity of radiotherapy either via the use of 3D conformal radiotherapy and dose escalation (6–8) or by the use of unconventionally fractionated radiotherapy (13–17, 23, 24).

The latter approach is not only important in our efforts to overcome the still high local failure rates after conventional radiotherapy, as shown by recent studies, but also can present interesting options for patients who cannot receive (or who refuse) chemotherapy combined with radiotherapy.

A number of unconventional schedules have been tested, including accelerated radiotherapy (AF), hyperfractionated radiotherapy (HF) mixed schedules of hyperfractionated accelerated radiotherapy (HART), and the continuous hyperfractionated accelerated radiotherapy (CHART). (13–17, 23, 34). In two of the studies, a three-time daily program gave accelerated hyperfractionation to gross tumor and conventional hyperfractionation to electively irradiated volumes (13, 15).

The last two schemes (HART and CHART) represent an interesting compromise that takes advantage of decreased doses per fraction, which could reduce long-term normal tissue morbidity (25) and shorten overall treatment time, which could counteract cancer cell repopulation (26). Data on kinetics in NSCLLC seem to indicate a rapid cell proliferation, at least in an important subset of tumors (27, 28).

In our scheme, a total dose of 63 Gy is given in 1.5 Gy twice-daily schedule, over an elapsed time of 29 days. Compared to a conventionally fractionated 2 Gy/fraction scheme, in which 63 Gy would be given in 44 days, the gain is 15 days. Assuming an average Tpot of 3 days, the overall gain would be approximately 10 Gy. Regarding late tissue damage, with an average α/β value of 3, decreasing the dose per fraction from 2 to 1.5 would represent a decrease in BED of approximately 20%.

Taking this into account in this admittedly limited series of patients, we suggest that in terms of tolerance and survival, our results are comparable to those of our previously reported combined modality protocols, the GOTHA I and II (Table 3), and are also comparable to other radiochemotherapy regimes.

Regarding tolerance, Grade III and IV acute mucositis-esophagitis was seen in 13% and 14% of patients, respectively, in HART and GOTHA I and II, and Grade III–IV lung toxicity was 4% and 6%, respectively. In other studies, using concomitant radiochemotherapy, Grade III–IV mucositis-esophagitis ranged from 10% to 53% and Grade III–IV lung toxicity was between 8–25% (29–31).

In the CHART trial, 19% of patients had their diet reduced to fluids compared to 3% of patients treated conventionally; however, regarding symptomatic pneumonitis, it was 19% in the conventional and 10% in the CHART group (17). In a trial from Duke University, where a HART regime was given to 73.6 Gy, at 1.6 and 1.25 Gy/fraction, Grade III esophagal toxicity was 19% and the 2-year actuarial rate of severe lung toxicity was 20% (14).

As shown in Table 3, median survival and 1-, 2-, and 3-year survival of this HART regime were fairly similar to those of GOTHA I and II, knowing that patients in HART were excluded from combination chemoradiotherapy studies (see Table 1), and they were on average older, with higher percentage of Stage IIIb disease and less favorable performance status (Table 2). In our series, the median survival of 16.8 months was better than the usual 9–12 months found in series of conventional radiotherapy alone, and is comparable to studies using combination radiochemotherapy (10, 29–31).

In the CHART trial, the experimental arm demonstrated a significant improvement in survival of 8% at 1 year and 9% at 2 years over the conventional arm (17).

In the Duke trial, median survival was 15.3 months and 2-year survival 46% (14). RTOG 83-11 protocol compared doses of 60.0, 64.8, and 69.6 Gy using 1.2 Gy b.i.d. (23).

Thereafter, 2 arms of 74.4 and 79.2 supplanted the lowest arms. The 69.6 Gy was significantly better in favorable patients than all other arms, with 1-year survival rate of 58% and 3-year rate of 20% (23).

In a study from Shanghai, in which a total dose of 74.3 Gy was applied in three daily fractions of 1.1 Gy, median survival was 22.6 months, and 1-, 2-, and 3-year actuarial survival was 72%, 47% and 28%, respectively (15).

Other studies seem to disclose less convincing results with unconventionally fractionated radiotherapy. In a combined RTOG-ECOG Phase III randomized trial, standard radiation arm was compared to induction chemotherapy followed by radiation, and to twice-daily radiotherapy consisting of 1.2 Gy per fraction b.i.d. to a total dose of 69.6 Gy (24). This study demonstrated a significantly superior survival in the chemotherapy plus radiotherapy arm, but there was no statistically significant difference between the conventional and hyperfractionated-accelerated arm (24).

Accelerated fractionation radiotherapy including concomitant boost was used in RTOG trials (32, 33). For 355 patients treated this way at doses of 63–70.2 Gy in 5–5.5 weeks, results disclosed a disappointing 9-month median survival, and a 2-year survival ranging from 6% to 21% (32).

It is evident that a simple comparison between pilot studies, large Phase II, and randomized trials can be very misleading due to different methodologies, selection bias, different patient populations, small numbers, and other factors.

Nevertheless, it is fair to say that the patients included in our HART study represented a subset with poor prognosis, inoperable NSCLC who could not be included in protocols of radiochemotherapy. In this regard, our radiotherapy scheme was well tolerated, presented the advantage of being given in 4 weeks only, and gave a rather encouraging 16.8-month median survival. Similar schemes deserve further investigation, and perhaps should be integrated also in combined modality protocols or in those including conformal radiotherapy with dose escalation.

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