ELSEVIER

Lung Cancer 11 Suppl. 3 (1994) S5–S8

LUNG CANCER

IASLC

Concomitant and alternating radiation therapy (RT) and chemotherapy (CT) for inoperable, M0, non-small cell lung cancers (NSCLC): a consensus report

R.O. Mirimanoff[a], P. Rubin[b], J.D. Cox[c], D. Gandara[d], D. Grunenwald[e], M. Hazuka[f], J. Jassem[g], R. Komaki[c], K. Mattson[h], S. McDonald[b], F. Mornex[i], M. Palazzi[j], J.J. Pavy[k], F. Reboul[l], E. Shaw[m], G. Storme[n], R. Stout[o], T. Sutedja[p], M.D. Trovo[q], E. Vokes[r], G. Zanelli[q]

[a]*Centre Hospitalier Universitaire Vaudois, CHUV, Lausanne, Switzerland*
[b]*Cancer Center, University of Rochester, Rochester NY, USA*
[c]*University of Texas M.D. Anderson Cancer Center, Houston, TX, USA*
[d]*University of California Davis Cancer Center, Sacramento, CA, USA*
[e]*C.M.C., Porte de Choisy, Paris, France*
[f]*University of Michigan, Ann Arbor, MI, USA*
[g]*Medical Academy, Gdansk, Poland*
[h]*University Hospital, Helsinki, Finland*
[i]*Centre Léon Bérard, Lyon, France*
[j]*Istituto Nazionale Tumori, Milan, Italy*
[k]*Hôpital Jean Minjoz, Besançon, France*
[l]*Clinique Ste-Catherine, Avignon, France*
[m]*Mayo Clinic, Rochester, MN, USA*
[n]*V.U.B., Brussels, Belgium*
[o]*Christie Hospital, Manchester, UK*
[p]*Free University Hospital, Amsterdam, The Netherlands*
[q]*C.R.O. Aviano and G.H., Pordenone, Italy*
[r]*University of Chicago, Chicago, IL, USA*

1. Introduction

The group agreed unanimously that at the present time, there are not enough data to recommend the use of concomitant or alternating RT/CT in daily practice. Until information from current clinical trials becomes available, concomitant or alternating CT/RT schemes should be reserved for clinical research. Thus, the rest of the report will focus on clinical trials only.

0169-5002/94/$07.00
SSDI 0169-5002(94)00367-V

2. Definition of concomitant and alternating regimen

A therapeutic scheme can be defined as concomitant when chemotherapy is delivered at the same time as radiotherapy. In alternating schedules CT and RT are rapidly alternated, and integrated in such a way that they are not administered together but still in close proximity. It was felt that alternating schedules should be discussed in conjunction with concomitant regimens because of common characteristics, such as a rather short overall treatment time.

3. Specific methods: definitions and endpoints relevant to concomitant or alternating RT/CT trials

3.1. Minimum requirements for reporting CT

There should be an exact description of the drug(s) with regard to dose, route of administration, exact duration (bolus vs. perfusion), time interval between CT and RT, report on dose intensity and supportive methods and therapies (antiemetics, antibiotics, growth factors, etc.).

3.2. Minimum requirements for reporting RT

There should be an exact description of the total dose, dose per fraction, daily dose (if more than 1 fraction/day), number of fractions, the interval between fractions, the number of treatment days per week, the total elapsed time, elective or unforseen interruptions, description of the technique, methods of calculations, including lung corrections, and of the irradiated volumes, using ICRU 50 criteria. Volumes of normal tissues (e.g. lung), dose histograms and V/Q test, are recommended.

3.3. Minimum requirements for assessing response/control

Chest X-rays are clearly insufficient and serial chest CAT scans should be obtained (see also Endpoints Committee Report).

3.4. Acute toxicity

A universally accepted grading systems (e.g. NCI/UICC) should be employed and clearly specified. At least all reactions equal or greater than Grade 3 should be recorded.

3.5. Late complications/reactions

These are defined as those that occur either after 90 days from the beginning of concomitant or alternated RT/CT or those occurring before but lasting beyond 90 days. As for acute toxicity, accepted grading systems should be employed and specified. The rate of complications should be given using a time-adjusted method (i.e. actuarial calculations). A new NCI late effects normal tissue (LENT) score which RTOG is developing with other cooperative groups is also being considered by EORTC and will be published soon.

3.6. Patterns of failure

Relapse pattern is critical for evaluating the effect of a combined modality. The minimum requirement is to report failures at least at 3 levels: T, N and M, and preferably as a combination of these (giving a total of seven possible combinations) (see also Endpoints Committee Report). Ideally, whenever a site of failure (such as distant metastasis) is noted, the patient should be regularly investigated for other possible concurrent and later sites of failures (such as local). Toxic and intercurrent deaths are to be recorded.

4. Current data

A large number of Phase I–II studies on concomitant (and to a lesser extent alternating) RT/CT have been published over the past 5 years, most of them using cisplatin alone or cisplatin-based combination chemotherapy. Three non-cisplatin randomized trials failed to show any improvement when combined modality was compared with RT alone, whereas of four cisplatin randomized trials, only one demonstrated a benefit in local control and survival. It is felt that if there is any improvement with concomitant CT/RT, it is modest and likely to be due to the use of cisplatin.

5. Recommendations for future clinical trials

5.1. Testing a chemotherapeutic agent as a radiosensitizer

If a study is designed to assess the radiosensitizing effect of an agent, such as cisplatin, it is recommended that (i) it should be clearly specified, and (ii) the RT control arm should correspond to a widely accepted current treatment (e.g. 60 Gy, 2 Gy/fractions daily).

5.2. Importance of local control (LC)

Since the last meeting, one major emerging point is that even with high dose RT (±CT), local control is low (~20%), certainly much lower than it had been thought previously, especially when local control was evaluated cytologically or histologically. Failing to achieve a local control is incompatible with cure. Since the majority (80%) of patients are not locally controlled, a CT regimen that would be efficient only on distant metastases would be of benefit in only on a minority of patients. Improving the local control is likely to have an effect on survival, and even possibly (according to recent models) on distant metastasis as well.

5.3. Possible methods for improving local control

In the context of concomitant or alternating treatment, LC could be improved by the following means: more agressive RT, currently tested multidrug combination CT with RT, new drugs and RT, cytokines and RT.

5.4. Possible methods for improving local control

In the context of concomitant or alternating treatments, LC could be improved

by the following means: more aggressive RT, currently tested multidrug combination of CT with RT, new drugs and RT, cytokines and RT.

5.5. Improving RT

Delivery of RT may be improved by newer technologies: 3D planning, conformal therapy, particle therapy, etc. Biological dose can be increased by the use of: new fractionations such as hyperfractionation, accelerated or hyperaccelerated fractionation, dose escalation, combined external beam and endobronchial brachytherapy, radiosensitizers, etc.

5.6. Current combinations of CT and RT

There are enough Phase II studies (some with encouraging results) on combination CT/RT so that the currently best combinations (such as cisplatin–etoposide) should be tested with concomitant or alternating RT versus RT alone in Phase III randomized trials.

5.7. New drugs and RT

There are a number of new agents which are active in NSCLC (e.g. Taxol, Taxotere, Navelbine, Edatrexate, Topotecan, CPT-11 and Gemcitabine) which should be tested first in Phase I concomitantly with RT, then in Phase II trials, with or without cisplatin.

5.8. Cytokines with RT

Amongst the various cytokines, some are known radiosensitizers and are being actively investigated. Results of a pilot study using RT associated with β-interferon in very advanced cases of NSCLC have shown high efficacy and unexpected long-term survivals. A Phase III RTOG clinical trial is in progress. However, another pilot study investigating γ-interferon and RT demonstrated substantial toxicity without apparent improvement in therapeutic index.

Phase I trials on various interferons (e.g. α-interferon) with RT, both with or without cisplatin are encouraged.

Other cytokines (interleukins, growth factors) may prove interesting, but the evidence is still anecdotal.

5.9. Laboratory

Research in cancer biology, such as cell kinetics, mechanisms of RT/CT resistance, interaction between chemical and biological radiation modifiers, should be actively pursued. Whenever results are found to be positive, concept should be further explored using clinical Phase I trials.