Eur J Cancer Clin Oncol, Vol. 23, No. 11, pp. 1577–1579, 1987.
Printed in Great Britain

0277–5379/87$3.00+0.00

Perspectives and Commentaries

Treatment of Small Cell Lung Cancer: Another Study On Alternating Chemotherapy

DAVID H. JOHNSON and F. ANTHONY GRECO

Division of Medical Oncology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, *U.S.A.*

(A COMMENT ON: Brinker H, Hindberg J, Hansen PV. Cyclic alternating polychemotherapy with or without upper and lower body irradiation in small cell anaplastic lung cancer. A randomized study. *Eur J Cancer Clin Oncol* 1987, **23**, 205–211.)

DURING the past 15 years, considerable progress has been made in the management of small cell lung cancer (SCLC) [1, 2]. Combination chemotherapy has become the cornerstone of treatment as most patients present with widely disseminated disease and are not benefited by surgery or radiotherapy alone [1, 2]. Unfortunately, the majority of patients with this neoplasm continue to die of lung cancer regardless of what form their treatment takes. A primary cause of treatment failure appears to be the emergence of drug-resistant cell lines during chemotherapy [3]. Based on a mathematical model, Goldie and Coldman have suggested that the administration of two, essentially comparable, chemotherapy regimens in rapid alternating fashion can maximize therapeutic benefit while minimizing toxicity to the host [3, 4]. This approach is popularly known as "non-cross resistant" chemotherapy. However, even before Goldie and Coldman published their mathematical rationale for non-cross resistant chemotherapy, several investigators were empirically testing its value.

Between 1981 and 1986 there were eight randomized trials evaluating non-cross resistant chemotherapy in SCLC [5–7]. The results of these studies have not been overly encouraging as none has demonstrated a major benefit in median or long-term patient survival [1, 5–7]. However, there have been major problems with almost all of these studies including that of Brinker *et al.* reported in this journal [8]. Very often the "non-cross resistance" of the two chemotherapy regimens had not been verified and was usually only potentially present on the basis of different mechanisms of drug action [1 ,5]. (In their article, Brinker *et al.* provide no evidence that the two regimens employed were non-cross resistant.) Also, in those studies which did attempt to evaluate the effectiveness of the "non-cross resistant" regimen, response rates were usually low, rarely complete and almost always of short duration. Furthermore, many studies failed to use an optimal scheduling of chemotherapy alternation according to the tenets of Goldie and colleagues [4, 5]. While three "non-cross resistant" chemotherapy studies have yielded a statistically significant improvement in median survival, the analysis of these studies has been called into question and the clinical significance of the reported survival differences has been minimal [5, 7].

Although not all the ramifications of non-cross resistant chemotherapy have been settled, it appears that other approaches to the treatment of SCLC will probably be necessary to markedly change current results in the near future [1, 5, 9]. Irradiation is unquestionably capable of effecting tumor shrinkage in SCLC and may be non-cross resistant with chemotherapy [1, 2]. Thus, it seems reasonable that incorporation of this treatment modality into chemotherapy regimens might improve survival outcome. Indeed, when thoracic irradiation has been added to chemotherapy, the long-term survival of limited-stage patients has been improved in some studies [1, 2]. However,

Accepted 16 December 1986.

relapses often take place outside the thorax and are obviously not affected by local, thoracic irradiation. Thus, wide-field or "systemic irradiation" may be a more effective method of utilizing radiotherapy in the management of SCLC.

Radiation to half- or whole-body fields has been tried in the treatment of SCLC partly because wide-field irradiation have proven useful in metastatic tumor and some lymphomas [2, 10]. Additionally, this form of "systemic irradiation" offers a 1–3 log cell kill that could substitute for a cycle of systemic chemotherapy [11]. The initial reports of Salazar and colleagues were sufficiently encouraging that several groups undertook prospective studies to test the value of hemibody irradiation (HBI) in SCLC [11–14]. In a randomized trial, Urtasan *et al.* treated patients with thoracic irradiation plus chemotherapy or thoracic irradiation plus upper and lower HBI without chemotherapy [14]. In limited stage patients the treatment regimens produced comparable results illustrating the activity of HBI. However, the survival of extensive-stage patients was substantially worse in the HBI arm (3.5 mo vs 10 mo) [14]. Mason *et al.* treated 14 SCLC patients with cyclophosphamide, methotrexate and lomustine plus local chest irradiation followed by upper HBI [13]. Maintenance therapy was initiated 6 weeks after completing upper HBI. Three of the 12 evaluable patients achieved a complete response (CR) to induction chemotherapy and an additional three patients achieved CR status after upper HBI. Nevertheless, the overall outcome in this study was poor as only two patients were able to receive additional chemotherapy following upper HBI and median survival was not improved compared to historical controls [13]. Several additional studies, including the one reported in this journal, also have not shown improved results combining chemotherapy and HBI and toxicity has been significant [2, 8, 10]. Therefore, it appears that wide-field irradiation is not of great benefit in the treatment of SCLC.

The treatment of SCLC continues to be a major challenge and is still in a state of evolution. Although the non-cross resistant regimens tested to date have failed to yield major therapeutic advances, the principle remains sound. If truly non-cross resistant regimens are identified, further investigation of this approach is clearly warranted. In the meantime, additional innovative treatment approaches such as "unconventional" fractionation radiotherapy schemes [15] or dose-intensification by means of frequent (e.g. weekly) administration of multiple active agents would appear to merit further investigation. Ongoing biological studies will hopefully provide additional therapeutic leads [1, 2].

REFERENCES

1. Johnson DH, Greco FA. Small cell carcinoma of the lung. *CRC, Crit Rev Oncol/Hematol* 1986, **4**, 303–336.
2. Morstyn G, Ihde DC, Lichter AS *et al.* Small cell lung cancer 1973–1983: early progress and recent obstacles. *Int J Radiation Oncol Biol Phys* 1984, **10**, 515–539.
3. Goldie JH, Coldman AJ. The genetic origin of drug resistance in neoplasms: implications for systemic therapy. *Cancer Res* 1984, **44**, 3643–3653.
4. Goldie JH, Coldman AJ, Gudauskas GA. Rationale for the use of alternating non-cross-resistant chemotherapy. *Cancer Treat Rep* 1982, **66**, 439–449.
5. Elliott JA, Osterlind K, Hansen HH. Cyclic alternating "non-cross resistant" chemotherapy in the management of small cell anaplastic carcinoma of the lung. *Cancer Treat Rev* 1984, **11**, 103–113.
6. Evans WK, Murray N, Feld R *et al.* Canadian multicenter trial comparing standard and alternating combination chemotherapy in extensive small cell lung cancer. *Proc Am Soc Clin Oncol* 1986, **5**, 169 (abstract).
7. Ettinger DS, Mehta CR, Abeloff MD *et al.* A randomized comparison of conventional chemotherapy with immediate alternation of non-cross resistant chemotherapy in extensive disease small cell lung cancer. *Proc Am Soc Clin Oncol* 1986, **5**, 170 (abstract).
8. Brincker H, Hindberg J, Hansen PV. Cyclic alternating polychemotherapy with or without upper and lower half body irradiation in small cell anaplastic lung cancer. A randomized study. *Eur J Cancer Clin Oncol* 1987, **23**, 205–211.
9. Aisner J, Alberto P. Bitran J *et al.* Role of chemotherapy in small cell lung cancer: a concensus report of the International Association for the Study of Lung Cancer Workshop. *Cancer Treat Rep* 1983, **67**, 37–43.
10. Lichter AS, Bunn PA, Ihde DC *et al.* The role of radiation therapy in the treatment of small cell lung cancer. *Cancer* 1985, **55**, 2163–2175.
11. Salazar OM, Rubin P, Keller BE *et al.* Systemic (half-body) radiation therapy. *Int J Radiat Oncol Biol Phys* 1978, **4**, 937–950.
12. Salazar OM, Creech RH, Rubin P *et al.* Half-body and local chest irradiation as consolidation following response to standard induction chemotherapy for disseminated small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1980, **6**, 1093–1102.
13. Mason BA, Richter MP, Catalano RB, Creech RB. Upper hemibody and local chest

irradiation as consolidation following response to high-dose induction chemotherapy for small cell bronchogenic carcinoma—a pilot study. *Cancer Treat Rep* 1982, **66**, 1609–1612.
14. Urtasan RC, Belch AR, McKinnon S, Higgins E, Saunders W, Feldstine M. Small-cell lung cancer: initial treatment with sequential hemi-body irradiation vs 3-drug systemic chemotherapy. *Br J Cancer* 1982, **46**, 228–235.
15. Peters LJ, Ang KK. Unconventional fractionation schemes in radiotherapy. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Important Advances in Oncology* 1986. Philadelphia, Lippincott, 1986, 269–286.