21. Moore MJ, Erlichman C, Thiessen JJ, *et al.* Variability in the pharmacokinetics of cyclophosphamide, methotrexate and 5-fluorouracil in women receiving adjuvant treatment for breast cancer. *Cancer Chemother Pharmacol* 1994, **33**, 472–476.
22. Morgan LR, Harrison EF, Hawke JE, *et al.* Toxicity of single- vs. fractionated dose ifosfamide in non-small cell lung cancer: a multicenter study. *Semin Oncol* 1982, **9**, 66–70.
23. Boddy AV, Wyllie R, Price L, Pearson ADJ, Idle JR. Increased clearance of ifosfamide in children during continuous infusion or repeated bolus administration. *Pharm Res* 1992, **9**, S314.
24. Boddy AV, Cole M, Pearson ADJ, Idle JR. The kinetics of the autoinduction of ifosfamide metabolism during continuous infusion. *Cancer Chemother Pharmacol* 1995, **36**, 53–60.
25. Kurowski V, Wager T. Comparative pharmacokinetics of ifosfamide, 4-hydroxyifosfamide, chloroacetaldehyde and 2- and 3-dechloroethylifosfamide in patients on fractionated intravenous ifosfamide therapy. *Cancer Chemother Pharmacol* 1993, **33**, 36–42.

Acknowledgements—This work was supported by grants from the North of England Cancer Research Campaign, North of England Children's Cancer Research Fund and ASTA Medica AG, Frankfurt, Germany. We would like to thank Prof. A.W. Craft for his support.

Pergamon

European Journal of Cancer Vol. 31A, No. 5, pp. 790–793, 1995
Elsevier Science Ltd
Printed in Great Britain

0959-8049(94)E0124-M

Feature Articles

Therapy of Carcinoma of the Oesophagus: Either Attempt it Not or Succeed

J.A. Ajani

CARCINOMA OF the oesophagus is endemic in certain parts of China, Russia, Iran, Brazil, South Africa and France. However, in the western world, it remains uncommon accounting for approximately 1% of all malignancies. In the U.S.A., approximately 11 300 new cases and 10 200 deaths were estimated, in 1993, to be the result of carcinoma of the oesophagus and gastro-oesophageal junction [1]. Approximately half the patients have local-regional disease at diagnosis, while the other half have more widespread cancer, usually beyond potential cure. T3- or T4- and N-positive lesions, according to the TNM classification, are present in 70% of patients. Thus, the prognosis remains poor and the 5-year survival rates have remained under 10% for the past four decades.

An intriguing aspect of this malignancy has been the dramatic increase in the incidence of adenocarcinoma of the oesophagus and proximal stomach. Particularly in the U.S.A., this increase has been observed in the past 15 years, and has superseded the increases in non-Hodgkin's lymphoma, melanoma and brain tumours [2]. The incidence of squamous carcinoma of the oesophagus has declined. Adenocarcinoma of the oesophagus and gastrooesophageal junction appears to afflict predominantly Caucasian males in their 50s and early 60s. The lifestyle of patients developing adenocarcinoma appears different from that of patients with squamous cell carcinoma, in that alcohol and tobacco abuse are infrequent. Nevertheless, the aetiologic factors for this rapid rise in incidence of adenocarcinoma have not yet been determined. Similarly, an increase in adenocarcinoma of the upper gastrointestinal tract has also been reported in Europe [3–5].

Successful efforts in the detection and treatment of early carcinoma can substantially improve therapy outcomes. Faced with more advanced primary tumours in patients in the western world, surgery produces mediocre results, in need of much improvement. Surgery, however, results in a consistent cure rate approaching 15% [6, 7]. Many prominent surgical groups worldwide now favour radical lymphadenectomy, although this issue remains as unsettled for patients with carcinoma of the oesophagus as it is for patients with gastric carcinoma. Two obstacles define the failure of surgery to cure more patients: (i) a curative resection rate that varies from 55 to 65% (this is partly due to inadequacy of clinical staging), and (ii) subsequent distant as well as local relapses. The surgical mortality has declined over the past 15 years and remains well under 5% in the hands of the surgical groups that perform oesophageal surgery quite frequently. The Ivor-Lewis oesophagogastrectomy is preferred by more groups than the transhiatal approach.

Recent investigations with endoscopic ultrasonography have provided an accurate appraisal of tumour stage, particularly the T stage [8], compared to those obtained by either computerised tomography or magnetic resonance imaging. Substantial further improvements in staging will be slow, but will probably involve antibody-mediated imaging or positron emission tomographic scanning.

Radiotherapy has played a substantial palliative role in the management of carcinoma of the oesophagus. However, radiotherapy alone, given either prior to surgery, after surgery or as definitive therapy, has not demonstrated a consistent survival advantage for patients with local-regional carcinoma. Thus, radiotherapy alone is recommended only when the patient is not suitable for surgery, and chemotherapy is contra-indicated.

Correspondence to J.A. Ajani at the Department of Gastrointestinal Medical Oncology and Digestive Diseases, U.T.M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, Texas 77030-4095, U.S.A.
Received 22 Oct. 1993; accepted 2 Mar. 1994.

Most patients, particularly in the western hemisphere, have widely disseminated occult (or overt) metastases at diagnosis. This virulent natural history is further supported by autopsy reports [9, 10]. Therefore, treatment of the occult metastases must be considered in addition to that of local-regional carcinoma to achieve potential survival advantage. For this reason, the potential role of chemotherapy has assumed more emphasis.

The relative rarity of carcinoma of the oesophagus and severe local morbidity necessitating immediate intervention have hampered traditional drug development approaches in this disease. Approximately 15 chemotherapeutic agents have been adequately investigated [11]. The majority of these agents were studied in patients with squamous cell carcinoma of the oesophagus. One must consider the limitations imposed by the compilation of data from a number of studies reported over the past two decades. Nevertheless, approximately eight chemotherapeutic drugs emerge as active agents against carcinoma of the oesophagus, resulting in a $\geq$ 20% response rate. These agents are bleomycin, cisplatin, 5-fluorouracil (5-FU), methotrexate, methyl-GAG, mitomycin-C, paclitaxel and vindesine. Of the eight agents, only paclitaxel has been studied in a single clinical trial with an adequate number of patients with adenocarcinoma histology.

Among these, cisplatin, mitomycin-C, 5-FU and paclitaxel are likely to be further studied; use of methyl-GAG, vindesine, bleomycin, and methotrexate has declined. Cisplatin has been increasingly used in combination chemotherapy of squamous cell carcinoma [12–14] and adenocarcinoma of the oesophagus [15–17]. Severity of nausea and vomiting can be reduced by the use of new anti-emetic regimens and also by the use of multiple-day regimen of cisplatin (for example, 20 mg/m^2/day for 5 days in lieu of a single 100 mg/m^2 bolus). Mitomycin-C has been studied in combination with 5-FU and concurrently with radiotherapy in patients with adenocarcinoma of the oesophagus as well as squamous cell carcinoma.

Paclitaxel (Taxol) is a complex plant product (a diterpene) that has demonstrated significant clinical and preclinical activity against a variety of tumours and tumour models [18]. In an ongoing trial at the UT M.D. Anderson Cancer Center (Houston, Texas, U.S.A.) and the Memorial Sloan-Kettering Cancer Center (New York, U.S.A.), 43 patients have been treated (30 with adenocarcinoma and 13 with squamous cell carcinoma). Paclitaxel is administered at a starting dose of 250 mg/m^2 over 24 h every 21 days [19]. All patients also receive granulocyte colony-stimulating factor (G-CSF). The preliminary data suggest that paclitaxel is an active agent against both histological types (9 of 29 evaluable patients with adenocarcinoma have had a partial response, and 3 of 11 evaluable patients with squamous cell carcinoma have had a partial response). Paclitaxel is well tolerated. Combination studies of paclitaxel, particularly with 5-FU and cisplatin, are warranted and are being planned.

The issue of chemosensitivity differences between squamous cell carcinoma and adenocarcinoma has surfaced. Squamous cell carcinoma is chemotherapy-senstitive to cisplatin-based combination therapy resulting in a 50–60% partial remission rate. Limited numbers of studies in adenocarcinoma suggest that it is a relatively chemosensitive tumour with a partial response rate in the range of 30–40%. The other issue that remains unresolved is that of the natural history differences between squamous cell carcinoma and adenocarcinoma.

In patients with squamous cell carcinoma, only two regimens have been studied extensively and in an adequate number of patients. These two regimens include (i) bleomycin + cisplatin + vindesine and (ii) 5-FU + cisplatin. Bleomycin + cisplatin + vindesine has been studied in the largest number of patients and has resulted in a respectable response rate of approximately 48% [11]. This regimen has been currently abandoned in favour of 5-FU + cisplatin because of toxicity considerations. The combination of cisplatin + 5-FU has gained popularity for squamous cell carcinoma.

Combined modality therapy of carcinoma of the oesophagus has been modelled after investigations in head and neck carcinoma. All three modalities have been combined in all possible sequences, but only a few strategies have demonstrated a benefit and are likely to prevail.

Local control can be enhanced by the use of chemotherapy and concurrent radiotherapy. A high rate of pathological complete responses (up to 30%) has been documented in the past [20]. In a recently completed study, by RTOG (Radiation Therapy Oncology Group headquartered in Philadelphia, Pennsylvania, U.S.A.), patients with local-regional carcinoma (with either histology) were prospectively randomised to receive either 5-FU plus cisplatin concurrently with 50 or 64 Gy of radiotherapy alone [21]. In this study, patients with unresectable carcinoma or those who were medically unfit for surgery were included. 60 patients were randomised to radiotherapy alone and 61 patients were randomised to combined modality therapy. The median survival was 8.9 months for patients receiving radiotherapy alone as compared with 12.5 months for patients receiving combined modality therapy. Accrual on the radiotherapy alone arm was stopped once the interim analysis demonstrated significant survival advantage for patients receiving combined modality therapy. 73 additional patients were accrued on a non-randomised combined modality therapy arm and a recent analysis has demonstrated their median survival to be 14.5 months. The morbidity was substantial for patients receiving combined modality therapy and, in addition, the rate of persistent local disease or local relapse is also substantial in both arms, but more particularly in the radiotherapy alone arm. However, the value of the modest advantage in median survival as a result of combined modality has been debated, but follow-up at 24 months is revealing more gratifying results. Undoubtedly, more analysis of these data and a longer follow-up is necessary. Nevertheless, the use of 5-FU plus cisplatin concurrently with 50 Gy of radiotherapy is now being recommended for patients with unresectable squamous cell carcinoma.

In another randomised trial, conducted by ECOG (Eastern Cooperative Oncology Group), 130 patients with squamous cell carcinoma were treated [22]. All patients received 40 Gy of radiotherapy with or without 5-FU plus mitomycin-C, and then had the option of receiving surgical resection. Patients not having surgery received additional radiotherapy. The median survival was 9 months for those who received radiotherapy and 14.9 for those who received combined modality therapy. These data are yet to be published. Nevertheless, this is another study demonstrating a modest survival benefit as a result of chemoradiotherapy.

The value of preoperative concurrent chemotherapy and radiotherapy has not been demonstrated in controlled clinical trials. Several pilot studies have demonstrated a high rate of pathological complete response and an acceptable curative resection rate. Nevertheless, the pre-operative chemotherapy with concurrent radiotherapy results in significant morbidity and mortality [14, 23], which remains a substantial concern. An ongoing controlled trial at the University of Michigan in Ann

Arbor is comparing preoperative chemotherapy (5-FU, cisplatin and velban) plus hyperfractionated radiotherapy with surgery alone in patients with potentially resectable carcinoma of the oesophagus. A total of 90 patients have been entered at present (Mark Orringer, personal communication, August 1993). Thus, the routine use of pre-operative chemotherapy concurrently with radiotherapy for patients with potentially resectable carcinoma cannot yet be recommended.

The rationale for the use of pre-operative therapy has been described in previous reports [13–16, 24, 25]. Pre-operative approaches provide a unique opportunity to evaluate the true biological effects of any therapy by examining the pathological response. The most important parameters of the effectiveness of any treatment are a significant prolongation of the survival duration and an increase in the 5-year survival rate. The usefulness of expecting a 5–10% pathological complete response rate is to set a short-term study goal to allow a relatively rapid evaluation of regimens in a timely manner by treating approximately 30 patients. I favour this approach until effective combination chemotherapy is defined, at which point randomised controlled trials could be launched.

The other question is: how much chemotherapy is adequate? Previously, pre-operative studies have employed only one or two courses and most often no postoperative therapy [12, 14, 26]. We have demonstrated the feasibility of up to six courses of chemotherapy [15, 16]. Nearly all pilot studies utilising one or two courses of chemotherapy for local-regional carcinoma of the oesophagus have resulted in median survival durations in the range of 10–14 months. Although the ideal number of courses is not yet known, it is recommended that more than two courses of chemotherapy and perhaps as many as five be used.

Another issue to be considered is the tolerance of postoperative chemotherapy. It has been noted that patients have a poor tolerance to postoperative chemotherapy compared to pre-operative chemotherapy [14, 16,17, 25, 16]. We have recently demonstrated the feasibility of administering all five courses of chemotherapy pre-operatively [27] or prior to definitive chemoradiotherapy [15]. Chemotherapy doses can be maintained at a higher level than the doses which have to be reduced consistently for postoperative chemotherapy courses.

Currently, one randomised controlled trial is underway in the U.S.A. comparing pre-operative plus postoperative chemotherapy and surgery with surgery alone. Patients with local-regional carcinoma of the oesophagus who have potentially resectable lesions are eligible for this trial. Patients can have either squamous cell carcinoma or adenocarcinoma. Patients are stratified by histology and per cent weight loss ($\leq$ 10%). Patients randomised to chemotherapy receive three courses of 5-FU and cisplatin before surgery and two courses after surgery. The targeted accrual on this study is 444 patients and at present approximately 250 patients have been treated.

FUTURE DEVELOPMENTS AND CHALLENGES

Adenocarcinoma has become more common than squamous cell carcinoma in the U.S.A. This change will probably also occur in Europe and, perhaps at a much late date, in other continents. Sensitivity of adenocarcinoma to chemotherapy and radiotherapy is not yet fully defined. If it is significantly different to that of squamous cell carcinoma, then a new database will have to be developed.

Chemotherapy continues to contribute to the treatment of carcinoma of the oesophagus and is likely to assume a greater role. The combined modality therapy needs further refinement. New agents need to be found at a rapid pace and integrated in combination chemotherapy as well as with radiotherapy regimens. The strategy of administering all chemotherapy and in some cases chemotherapy plus radiotherapy prior to surgery merits further exploration.

Further research should be directed towards conducting phase II trials to discover new active chemotherapeutic (for example, paclitaxel and venorelbine) or biological agents. In addition, development of combination chemotherapy with a low toxicity profile and a 5–10% pathological complete response rate is desirable. Studies of newer radioenhancers in conjunction with radiotherapy must be conducted. Development of concurrent chemotherapy and radiotherapy combinations that might result in lower morbidity and mortality when given pre-operatively would be of importance. Finally, I believe we are slowly inching towards a trial that would compare surgery with definitive chemoradiotherapy. However, this trial will only be fruitful if effective systemic therapy is established to control or eliminate occult metastases. Thus, many exciting challenges lie ahead. It is, however, up to us to take on these challenges: *either attempt it not or succeed.*

1. Boring CC, Squires TS, Tong T. Cancer statistics, 1993. *CA Cancer J Clin* 1993 **43**, 7–26.
2. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991 **265**, 1287–1289.
3. Levi F, La Vecchia C. Adenocarcinoma of the esophagus in Switzerland (letter). *JAMA* 1990, **265**, 2960.
4. Powell J, McConkey CC. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. *Br J Cancer* 1991, **62**, 440–443.
5. Reed PI. Changing pattern of esophageal cancer. *Lancet* 1991 **338**, 178.
6. Müller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. *Br J Cancer* 1990 **77**, 845–857.
7. Siewert JR. Esophageal cancer from the German point of view. *Jpn J Surg* 1989, **19**, 11–20.
8. Rösch T, Lorenz R, Zenker K, *et al.* Local staging and assessment of resectability in carcinoma of the esophagus, stomach, and duodenum by endoscopic ultrasonography. *Gastrointest Endosc* 1992, **38**, 460–467.
9. Anderson LL, Lad TE. Autopsy findings in squamous-cell carcinoma of the esophagus. *Cancer* 1982, **50**, 1587–1590.
10. Bosch A, Frias Z, Caldwell WL, Jaeschke WH. Autopsy findings in carcinoma of the esophagus. *Acta Radiol Oncol* 1979, **18**, 103–112.
11. Ajani JA. Contribution of chemotherapy in the treatment of carcinoma of the esophagus: Results and commentary. *Semin Oncol* 1994, in press.
12. Kelsen D, Hilaris B, Coonley C, *et al.* Cisplatin, vindesine, and bleomycin chemotherapy of local-regional and advanced esophageal carcinoma. *Am J Med* 1983, **75**, 645–652.
13. Kelsen DP, Fein R, Coonley C, Heelan R, Bains M. Cisplatin, vindesine, and mitoguazone in the treatment of esophageal cancer. *Cancer Treat Rep* 1986, **70**, 255–259.
14. Forastiere AA, Gennis M, Orringer MB, Agha FP. Cisplatin, vindesine, and mitoguazone chemotherapy for epidermoid and adenocarcinoma of the esophagus. *J Clin Oncol* 1987, **5**, 1143–1149.
15. Ajani JA, Ryan B, Rich TA, *et al.* Prolonged chemotherapy for localized squamous carcinoma of the esophagus. *Eur J Cancer* 1992, **28A**, 880–884.
16. Ajani JA, Roth JA, Ryan B, *et al.* Evaluation of pre- and postoperative chemotherapy for resectable adenocarcinoma of the esophagus or gastroesophageal junction. *J Clin Oncol* 1990, **8**, 1231–1238.
17. Ajani JA, Roth JA, Ryan MB, *et al.* Intensive preoperative chemotherapy with colony-stimulating factor for resectable adenocarcinoma of the esophagus or gastroesophageal junction. *J Clin Oncol* 1993, **11**, 22–28.
18. Wani MC, Taylor HL, Wall ME, *et al.* Plant antitumor agents VI. The isolation and structure of Taxol, a novel antileukemic and

antitumor agent from taxus brevifolia. *J Am Chem Soc* 1971, **893**, 2325–2327.
19. *NCI. Phase II Study of Taxol and Granulocyte–Macrophage Colony Stimulating Factor in Patients with Advanced Squamous Cell Carcinoma and Adenocarcinoma of the Esophagus.* NCI Protocol-T92-0119; Ajani JA, Coordinating Principal Investigator.
20. Steiger Z, Franklin R, Wilson RF, *et al.* Complete eradication of squamous cell carcinoma of the oesophagus with combined modality chemotherapy and radiotherapy. *Am Surg* 1981, **47**, 95–98.
21. Herskovic A, Martz K, Al-Sarraf M, *et al.* Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the oesophagus. *N Engl J Med* 1992, **326**, 1593–1598.
22. Sischy B, Haller D, Smith T, Dayal Y, Schutt A, Hinson J. Interim report of EST 1282 phase III protocol for the evaluation of combined modalities in the treatment of patients with carcinoma of the esophagus, state I and II. *Proc Am Soc Clin Oncol* 1990, **9**, 105.
23. Leichman L, Steiger Z, Seydel HG, *et al.* Preoperative chemotherapy and radiation therapy for patients with cancer of the esophagus: a potentially curative approach. *J Clin Oncol* 1984, **2**, 75–79.
24. Ajani JA, Ota DM, Jessup JM, *et al.* Resectable gastric carcinoma: an valuation of pre- and postoperative chemotherapy. *Cancer* 1991, **68**, 1501–1506.
25. Ajani JA, Mayer RJ, Ota DM, *et al.* Preoperative and postoperative combination chemotherapy for potentially resectable gastric carcinoma. *J Natl Cancer Inst*, 1993, **85**, 1839–1844.
26. Hilgenberg AD, Carey RW, Wilkins EW, Choi NC, Mathisen DJ, Grillo HC. Preoperative chemotherapy, surgical resection, and selective postoperative therapy for squamous cell carcinoma of the esophagus. *Ann Thorac Surg* 1988, **45**, 357–363.
27. Ajani JA, Roth JA, Putnam JB, *et al.* Feasibility of five courses of preoperative chemotherapy in patients with resectable adenocarcinoma of the esophagus or gastroesophageal junction. *Proc Am Assoc Cancer Res* 1992, **33**, 218 (abstract no. 1306).

Pergamon

European Journal of Cancer Vol. 31A, No. 5, pp. 793–799, 1995

0959–8049/95 $9.50+0.00

0959-8049(95)00089-5

Cutaneous T-cell Lymphoma: Molecular Genetics, Immunology and Pathogenesis

U. Reinhold and H. Abken

INTRODUCTION

NON-HODGKIN'S LYMPHOMAS (NHL) includes a group of neoplasms that share a common target tissue, i.e. lymphoid cells. This group is characterised by a high degree of biological and clinical heterogeneity. Besides the spleen and lymph nodes, NHL may develop in extranodal organs which may be related to physiological extranodal lymphocytic migration within the normal immune system. The primary localisations of NHL in the skin represents one of the most common localisation of extranodal NHL [1]. The majority of cutaneous lymphomas derive from T-cell lineage whereas most nodal NHLs derive from B-cell lineage. The term cutaneous T-cell lymphoma (CTCL) was first used by Lutzner and associates in 1975 and has become widely accepted [2]. Most cases of CTCL are characterised by a malignant proliferation of $CD4^+$ helper T lymphocytes [3, 4]. However, a few cases have been described in which the neoplastic cells express a suppressor/cytotoxic or $CD8^+$ T-cell phenotype [5]. The prototype of CTCL is the cerebriform T-cell lymphoma, which is historically subdivided into mycosis fungoides (MF) and Sezary syndrome (SS). MF typically presents as cutaneous patches that can progress to infiltrated plaques and ultimately cutaneous tumours with lymphoid and visceral involvement. In SS, there is involvement of blood, lymph nodes, spleen, liver and skin associated with erythroderma and typically sparing of bone marrow. The tumour cells show characteristic, cerebriform nuclei (Sezary cells) and have a predilection for involvement of epidermis, either individually or in clusters referred to as Pautrier microabscesses [6]. CTCL other than MF/SS represent a rather heterogeneous group of cutaneous lymphomas which differ in morphology, immunopathology and clinical course of the disease [7–10]. At present, there is no concensus on a definition and terminology of these lymphomas. Our present use of CTCL designation may include MF, SS, small to medium pleomorphic T-cell lymphoma, medium to large pleomorphic T-cell lymphoma $CD30^+$ large cell anaplastic lymphoma and T immunoblastic lymphoma (Table 1).

MOLECULAR GENETICS

Malignant cells in CTCL harbour an abnormal karyotype, either widely heteroploid or hyperdiploid or pseudoploid, with

Table 1. Classification of primary cutaneous T-cell lymphomas

Mycosis fungoides
Sezary syndrome
T-pleomorphic lymphoma, small to medium
T-anaplastic large cell lymphoma
T-pleomorphic lymphoma, medium to large
T-immunoblastic lymphoma

Correspondence to U. Reinhold at the Department of Dermatology, University of Bonn, Sigmund-Freud Straße 25, 53105 Bonn, Germany. H. Abken is at the Department of Internal Medicine, Laboratory for Tumorgenetics and Cell Biology, University of Cologne, Germany.
Recieved 24 Jan. 1995; accepted 7 Feb. 1995.