predominantly found in visceral sites in patients having radical or modified radical mastectomies. The propensity of visceral metastases in patients having radical or modified mastectomies in our study is of concern as this is not a common finding. A former report by Valagussa and colleagues emphasised that the sites of first relapse after radical mastectomies were documented to occur preferentially in distant organs and tissues [5]. In another large series, locoregional recurrences and distant metastases were present in 24% and 49% of patients, respectively, 10 years after a radical mastectomy [6].

In the light of the aforementioned studies, a question arises: does surgery enhance the spread of metastases in breast carcinoma? Metastatic capacity depends in part on angiogenesis, in which tumours induce the formation of new blood vessels which provide nutrients for tumour growth and create access to circulation for metastasis. If breast tumours are secreting potent angiogenesis inhibitors and this secretion ceases after surgery, the surgery is a real challenge for metastatic spread. However, to penetrate the extracellular matrix, the metastatic cells need to disrupt the basement membrane with proteinases. One could speculate that surgery may augment disruption of the basement membrane. Once tumour cells enter the stroma, they can gain easy access to lymphatics and blood vessels for further dissemination. Currently, we do not know the correct answer, but future studies are awaited to clarify the effect of surgery on metastases in breast carcinoma.


1. Bonadonna G. Current and future trends in the multidisciplinary approach for high-risk breast cancer. The experience of the Milan Cancer Institute. *Eur J Cancer* 1996, **32A**, 209–214.
2. Gündüz N, Fisher B, Saffer EA. Effect on surgical removal on the growth and kinetics of residual tumor. *Cancer Res* 1979, **39**, 3861–3865.
3. Fisher B, Gündüz N, Saffer EA. Influence of the interval between primary tumor removal and chemotherapy on kinetics and growth of metastases. *Cancer Res* 1983, **43**, 1488–1492.
4. Barışta İ, Baltali E, Güllü IH, *et al.* Factors influencing the distribution of metastases and survival in metastatic breast carcinoma. *Am J Clin Oncol,* in press.
5. Valagussa P, Bonadonna G, Veronesi U. Patterns of relapse and survival following radical mastectomy. Analysis of 716 consecutive patients. *Cancer* 1978, **41**, 1170–1178.
6. Lacour J, Le M, Caceres E, Koszarowski T, Veronesi U, Hill C. Radical mastectomy versus radical mastectomy plus internal mammary dissection. Ten year results of an international cooperative trial in breast cancer. *Cancer* 1983, **51**, 1941–1943.


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# 13-*Cis*-retinoic Acid and Alpha-interferon in Advanced Squamous Cell Cancer of the Oesophagus

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RETINOIDS, a class of compounds related to vitamin A, normally play a role in growth, vision, epithelial cell differentiation, and immune function [1]. A preventive effect of vitamin A on the development of chemically induced tumours has been demonstrated, as well as a therapeutic effect in cancer [2]. Cytokines, such as interferons, have demonstrated a synergistic effect with retinoids on the inhibition of proliferation in squamous cell carcinomas of the cervix, head and neck, and skin [3]. Here, we report the results of a phase II study of 13-*cis*-retinoic acid plus interferon alpha-2A in patients with metastatic squamous cell carcinoma of the oesophagus.

All patients were required to have measurable disease; age $\leqslant 75$ years; no prior chemotherapy; performance status (WHO) 0–2; life expectancy >3 months. Treatment consisted of interferon alpha-2A (IFN-α, Roferon-A$^R$, Roche) s.c. $3 \times 10^6$ IU every day, plus 13-*cis*-retinoic acid (cRA, isotretinoin, Roaccutan$^R$, Roche) orally 1 mg/kg/day. Treatment was continued for at least 2 months in all patients, unless disease progressed earlier, and for at least 3 months in case of no change, unless toxicity was intolerable. Response and toxicity were evaluated according to WHO criteria.

10 patients entered the study, all evaluable. The median duration of treatment was 8 weeks (range 4–33 weeks). One patient discontinued treatment after 4 weeks because of overt progressive disease. The patient characteristics are shown in Table 1.

No or very mild nausea (WHO grade 0, 1) was present in 9 patients, grade 2 in 1 patient. 2 patients developed grade 1 leucopenia, and nearly all patients showed a slight but discernible decrease in platelets, but still within the normal range (WHO 0). In 1 patient, the dose of cRA was reduced to 0.5 mg/kg/day because of difficulty in swallowing, and a dry and moderately painful skin. A dry skin was noted in 8 patients (WHO 1). Fatigue was seen only during the first 1 or 2 weeks after the start of treatment. No elevations of serum transaminases could be detected.

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*Table 1. Patient characteristics (n = 10)*

| | |
|---|---|
| Sex | |
| Male | 6 |
| Female | 4 |
| Median age (years) | 59 (35–73 years) |
| WHO performance status | 1 (range 0–2) |
| Weight loss (%) | |
| Unknown | 2 |
| 1–5 | 2 |
| 6–10 | 3 |
| 11–20 | 3 |
| Extent of disease | |
| Metastatic | 3 |
| Locoregional and metastatic | 7 |
| Localisation of tumour sites | |
| Lymph nodes | 11 |
| Lungs | 2 |
| Liver | 5 |
| Other | 1 |
| Pretreatment | |
| Oesophageal resection | 3 |

Treatment was discontinued because of progression ($n = 8$) or poor general performance status ($n = 2$).

No objective responses were seen. Two patients had stable disease for a duration of 2 and 10 months. All patients have died. The median survival was 8.8 months (range 3.6–14.9 months) after start of treatment.

In this study, no objective responses to the combination of cRA and IFN-α were seen (95% confidence interval: 0–31%). One patient experienced stabilisation of the disease for a period of 10 months. The toxicity of this regimen was mild. Recent clinical studies in squamous cell cancer of the skin and cervix have demonstrated greater antitumour activity of the combination of cRA and IFN-α, compared with either agent alone [4, 5], although two phase II studies in advanced non-small-cell lung cancer could not confirm these results: 2 PRs in 58 patients [6, 7]. Toma and colleagues reported on 2 patients with oesophageal cancer; both achieved complete remission after treatment with IFN-α $6 \times 10^6$ IU every day and cRA 1 mg/kg/day with a response duration of 8 and 36 months, respectively [8]. In our study, the IFN-α dose was $3 \times 10^6$ IU per day, and a second difference may be the stage of disease; 7 of our patients had bulky disease at the start of treatment with the primary tumour still *in situ*.


1. Meyskens F, Goodman G, Alberts D. 13-*cis*-Retinoic acid: pharmacology, toxicology, and clinical applications for the prevention and treatment of human cancer. *Crit Rev Oncol Hematol* 1987, **3**, 75–101.
2. Bollag W. Vitamin A and vitamin A acid in the profylaxis and therapy of epithelial tumours. *Int J Vit Res* 1970, **40**, 299–314.
3. Smith MA, Parkinson DR, Cheson BD, Friedman MA. Retinoids in cancer therapy. *J Clin Oncol* 1992, **5**, 839–864.
4. Lippman SM, Parkinson DR, Itri LM, *et al.* 13-*cis*-Retinoic acid and interferon alpha-2a: effective combination therapy for advanced squamous cell carcinoma of the skin. *J Natl Cancer Inst* 1992, **84**, 235–241.
5. Lippman SM, Kavanagh JJ, Paredes-Espinoza M, *et al.* 13-*cis*-Retinoic acid plus Interferon α-2a: highly active systemic therapy for squamous cell carcinoma of the cervix. *J Natl Cancer Inst* 1992, **84**, 241–245.
6. Rinaldi DA, Lippman SM, Burris HA, Chon C, Von Hoff D, Hong WK. Phase II study of 13-*cis*-retinoic acid and interferon-α-2a in patients with advanced squamous cell lung cancer. *Anticancer Drugs* 1993, **4**, 33–36.
7. Arnold A, Ayong J, Douglas L, *et al.* Phase II trial of 13-*cis*-retinoic acid plus interferon α in non small cell lung cancer. *J Natl Cancer Inst* 1994, **86**, 306–309.
8. Toma S, Palumbo R, Vincenti M, *et al.* Efficacy of recombinant alpha-interferon 2a and 13-*cis*-retinoic acid in the treatment of squamous cell carcinoma. *Ann Oncol* 1994, **5**, 463–465.


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# Oral Tegafur and Folinic Acid for the Treatment of Advanced Colorectal Cancer

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TEGAFUR (TG) is a fluoropyrimidine precursor of 5-fluorouracil (5-FU). It is given orally for prolonged periods in divided doses to simulate a protracted continuous infusion of 5-FU. The activity of orally administered TG is similar to that of intravenous 5-FU in advanced colorectal cancer, with superimposable response and survival results as shown in several comparative trials [1, 2], but with the added advantage of oral administration, an important consideration to improve the quality of life of the patients receiving this palliative therapy. As for toxicity, it is also similar to that of continuous infusion 5-FU, with predominant digestive toxicity and minimal myelosuppression. Several phase II studies in advanced colorectal cancer have been reported [3, 4]. The most widely used schedule was TG 1 gr/m$^2$/day orally for 21 days every 4 weeks, although alternative schedules with different doses and duration have also been tested. 5-FU can be modulated by folinic acid (FA) with a higher response rate in colorectal carcinoma demonstrated in previous studies [5, 6]. Few studies of oral therapy with

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