PAPERS AND SHORT REPORTS

Multimodal treatment in operable breast cancer: five-year results of the CMF programme

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Abstract

The five-year results of a prospective randomised trial of radical mastectomy (179 patients) versus radical mastectomy followed by adjuvant chemotherapy (207 patients) were analysed. Chemotherapy consisted of 12 monthly cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF). Both relapse-free survival (controls 44.6%, CMF group 59.5%) and total survival (controls 66.2%, CMF group 78.4%) were significantly improved. The findings were related to the number of diseased axillary nodes and amount of drug administered, and were independent of CMF-induced amenorrhoea. Menopausal state alone appeared to affect the five-year results only when the amount of drug administered was not taken into account. Salvage treatment at first relapse failed to improve total survival in the controls compared with the CMF group. Acute toxic manifestations were moderate and reversible. Chronic organ damage and increased incidence of second neoplasms (controls 1.7%, CMF group 1.4%) were not observed.

The multimodality approach to treatment of primary breast cancer is a new and important advance. This and other studies are continuing.

Introduction

In June 1973 we began a prospective randomised study of women with operable breast cancer utilising combined chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF). Our aim was to find whether prolonged administration of CMF after operation would alter the rates of relapse-free survival and total survival in patients with metastatic deposits in axillary lymph nodes, who are at high risk of early recurrence

after surgery.¹ At the time the standard primary treatment for resectable breast carcinoma was radical surgery with or without postoperative irradiation, which were yielding a plateau of therapeutic results.² Combined-modality treatment was known to be effective in experimental animals,³ while in clinical cancer this approach had been successful only in some paediatric neoplasms. In breast cancer, however, initial attempts with adjuvant single-agent chemotherapy had given inconsistent results,⁴ and none of the published reports was conclusive.

Preliminary findings of the adjuvant CMF programme⁵⁻⁷ and of similar studies⁸⁻⁹ suggested that the new strategy was correct and worthy of more-widespread attention. The true efficacy of any treatment for operable breast cancer is best represented by the results at 10 years. We, however, present our results at five years in an attempt to show that the multimodality approach with cyclical combination chemotherapy is a new, important advance in the primary management of mammary carcinoma.

Subjects and methods

The trial was initiated on 1 June 1973, and patients were collected consecutively up to 11 September 1975. All of the women received their surgical and medical treatment and regular follow-up examinations at this institute. The criteria for inclusion in the trial have been detailed elsewhere.⁵⁻⁶ Briefly, eligible patients had potentially curable breast cancer (TNM classification T_{1a}-T_{3a}T_{3a}; N₀-N_{1a}-N_{1b}, M₀), histologically proved metastases in axillary lymph nodes, and no evidence of disease in distant sites. They lived close enough to the institute to receive chemotherapy and attend for regular follow-up. Adequate bone marrow reserve as well as normally functioning liver and kidneys were also required. Women over 75 or suffering from other malignancies (except curable skin cancer) or major, non-neoplastic diseases were excluded.

TREATMENT

All patients were subjected to either Halsted or extended radical mastectomy. No postoperative radiotherapy was given. Within four weeks after operation patients were allocated at random either to no further treatment or to receive CMF for 12 consecutive cycles. We used the technique of block randomisation (permuted block of length 4 for two treatments). Before being allocated to either group patients

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were stratified according to type of operation (Halsted or extended mastectomy), age (up to 50 or over 50), and number of axillary lymph nodes affected (one to three or over three). A total of 179 women were allocated to no further treatment (controls) and 207 to CMF. Most of the patients in the two groups had presented with ductal infiltrating carcinoma (88% of controls, 87% of the CMF group), T_2 primary tumour (76% and 74%), and one to three axillary lymph nodes affected (70% and 68%). About three-quarters of the women were subjected to Halsted mastectomy (73% and 71%), and half were premenopausal (48% and 50%). Protocol deviation accounted for 14% of patients treated with chemotherapy.

The dose schedule of CMF was cyclophosphamide 100 mg/m² by mouth from day 1 to day 14, methotrexate 40 mg/m² intravenously on days 1 and 8, and fluorouracil 600 mg/m² intravenously on days 1 and 8. No drug was administered from day 15 to day 28. In 63% of women aged over 60 the initial doses of methotrexate and fluorouracil were reduced to 30 mg/m² and 400 mg/m² respectively. During treatment a dose-reduction schedule was applied to all patients with myelosuppression detected on days 1 and 8 of each treatment cycle. All three drugs were reduced by half when the leucocyte count was in the range 3.9×10^9 to $2.5 \times 10^9/l$ (3900 to 2500/mm³) or the platelet count in the range 129×10^9 to $75 \times 10^9/l$ (129 000 to 75 000/mm³). In more severe myelosuppression treatment was delayed until at least half of the dose could be administered. Toxic manifestations other than myelosuppression—for example, mucositis or cystitis—required temporary dose reduction only if severe.

Treatment failure was accurately assessed by clinical, radiological, and, whenever feasible, histological examination of the site(s) of first relapse. All radiographs were repeatedly reviewed by a team of radiologists and once also by external reviewers to confirm the presence and exact timing of recurrence. At the first relapse treatment was uniform for both groups of women, and systemic treatment—namely, chemotherapy with or without endocrine treatment—was used whenever possible. CMF was the first-line treatment for the controls, while Adriamycin (doxorubicin) plus vincristine¹⁰ was administered to the CMF-treated patients. A patient who refused cytotoxic therapy was given systemic treatment whenever possible, utilising hormonal manipulation according to age.

FOLLOW-UP STUDIES

Follow-up included clinical and radiological examinations at scheduled times. During the first year after mastectomy physical examination was repeated monthly, then every three months. Chest radiography was performed every three months and skeletal survey and liver scan every six months. From the end of the third year after mastectomy clinical examination and chest radiography were reduced to intervals of four to six months. Renal and liver function values were determined every three months during chemotherapy and then every six months. Additional examinations were carried out in the presence of symptoms and signs attributable to metastatic cancer or for suspicious x-ray findings. Oestrogen-receptor determination in the primary tumour and serial bone scans were not performed routinely.

STATISTICAL

Statistical analysis included relapse-free survival and survival distributions calculated with actuarial life-table methods, taken from the date of radical mastectomy to the closing date for analysis (1 February 1980). The proportion of patients relapse-free or surviving are given for one point in time (five years), as derived from life-table plots. Probabilities represent comparison of the entire plots and were calculated using the log-rank test and values of significance.¹¹

Results

RELAPSE-FREE AND TOTAL SURVIVAL

In each group of women the median duration of follow-up after mastectomy was 60 months. Figure 1 shows that the comparative relapse-free survival rate at five years was significantly higher in the CMF group than in the controls (59.5% v 44.6%; $p=0.0005$). In the controls the median time to relapse was 35 months, while this had not been reached in the CMF-treated women. Figure 2 shows the overall survival rates. At five years 78.4% of patients given CMF and

FIG 1—Comparative five-year relapse-free survival rates in patients treated with radical mastectomy alone (controls) and radical mastectomy plus CMF (CMF group).

FIG 2—Comparative five-year overall survival.

66.2% of controls remained alive. This difference was significant ($p=0.04$).

Analysis of the effects of other variables showed that whereas the type of operation failed to influence outcome, the number of axillary nodes affected was important in both groups (fig 3). Relapse-free survival was greater in women with one to three nodes affected (CMF group 69.4%, controls 48.1%; $p<0.0005$) than in those with more than three diseased nodes. In this second subgroup, however, the median time to relapse was considerably longer among the CMF-treated women (42 months) than among the controls (16 months), the difference being close to statistical significance. Figure 4 compares the effects of CMF in premenopausal and postmenopausal women. A significant improvement in relapse-free survival was evident in premenopausal women (CMF group 65.9%, controls 43.4%; $p<0.0005$) but not in postmenopausal women ($p=0.22$). Analysis of the relation between CMF-induced amenorrhoea and relapse-free survival in two major age groups failed to detect any therapeutic advantage for women with ovarian failure (table I).

A possible relation between the effect of CMF and the amount of the drug actually administered was investigated in successive analyses.¹² Premenopausal patients received more of each drug (74% of the planned dose) than did the postmenopausal patients (62%) owing to the initial dose reduction in women over 60. Relapse-free survivals were analysed separately in premenopausal and postmenopausal women given 85% or more of the planned dose, 84–65%, and less than 65%. Within each dosage subgroup premenopausal and postmenopausal women were comparable for known prognostic factors—that is, size of primary tumour and extent of nodal disease. Table II shows that there was a definite dose-response effect, and at each dosage the five-year relapse-free survival was similar in the two

menopausal groups. Furthermore, in women who received low-dose CMF (less than 65% of the planned dose) the relapse-free survival was similar to that of controls.

Table III shows the relapse-free survival and total survival related to age. Although the subgroups were small, and with the possible exception of patients over 65, at each decade of age therapeutic results were apparently better with CMF. Nevertheless, the extent of nodal disease was not always evenly distributed in each age group, so that low-dose chemotherapy as well as the prevalence of three or more affected nodes in the CMF group may have been more important than age over 65.

SITE OF FIRST RELAPSE

No substantial difference in the pattern of treatment failure was evident between the control and CMF-treated groups. Local and

FIG 3—Comparative five-year relapse-free survival rates related to number of axillary lymph nodes affected.

FIG 4—Comparative five-year relapse-free survival rates related to menopausal state.

TABLE I—Five-year relapse-free survival in premenopausal women related to age and drug-induced amenorrhoea

		Age ≤40		Age >40	
		%	p	%	p
Total controls	..	22.5	0.04	48.1	<0.005
Total CMF-treated women	..	41.6		71.0	
Amenorrhoea	..	42.1	0.57	73.1	0.47
No amenorrhoea	..	41.3		75.0	

TABLE II—Relation between dosage of CMF and relapse-free survival (RFS)*

		Percentage of planned dosage given					
		≥85		84-65		<65	
		No of patients	RFS (%)	No of patients	RFS (%)	No of patients	RFS (%)
Total	..	41	78	94	57	72	45
Premenopausal	..	27	78	57	58	19	49
Postmenopausal	..	14	74	37	55	53	44

*Relapse-free survival at five years derived from life-table plots. RFS in controls: total 45%, premenopausal 43%, postmenopausal 49%.

TABLE III—Five-year relapse-free survival (RFS) and total survival according to age

Age (years)	Controls			CMF-treated women		
	No at risk	RFS (%)	Total survival (%)	No at risk	RFS (%)	Total survival (%)
≤35	7	14	38	15	60	73
36-45	45	51	71	50	59	79
46-55	63	42	65	70	62	79
56-65	34	49	72	50	55	73
>65	30	52	76	22	36	63

TABLE IV—Comparative overall results in patients treated with mastectomy alone (controls) or mastectomy plus CMF

		At first relapse*		Median survival in patients with relapse* (months)	
		Complete response + partial response (%)	Median duration of response (months)	From first relapse	From radical mastectomy
Controls	..	49	10	38	55
CMF group	..	41	10	30	50

*After chemotherapy.

regional recurrence alone occurred in 21 (11.7%) of the patients treated with surgery only and in 18 patients (8.7%) given CMF. Local and regional plus distant recurrence occurred in 11 (6.1%) and 3 (1.4%) patients in the two groups, while distant metastases alone occurred in 67 (37.4%) and 63 (30.4%) of the patients respectively. Of the two groups with distant metastases, four and five of the patients respectively had carcinoma in the opposite breast.

SECONDARY TREATMENT

For first relapses 91.3% of the controls and 93.9% of the CMF-treated patients were given systemic treatment. In over 80% of cases (83.6% of the controls, 85.5% of the CMF group) the treatment was monitored by the institute. Chemotherapy was given to about 60% of patients in both groups and consisted of CMF or CMF-derived combinations in most of the controls and Adriamycin plus vincristine in most of the adjuvant-treatment group. In addition, chemotherapy was supported with endocrine manipulation in 10.8% of the controls and 6.0% of the CMF-treated women. Endocrine treatment alone was employed when a patient refused cytotoxic agents and for specific clinical reasons (poor general condition, age over 65). Some 20.6% of controls and 28.9% of women in the adjuvant-treatment group received endocrine treatment alone. The remaining patients (about 8% in both groups) received only local irradiation or supportive treatment or both, mainly because of refusal of further anticancer treatment, pattern of relapse, including brain metastases, or poor general condition due to widespread disease. Rate and duration of response in patients adequately treated with chemotherapy were comparable (49% of controls, 41% of the CMF group; median duration 10 months in both groups). Thus since secondary treatment failed to alter the clinical course in either group, the difference in overall survival was mainly related to the primary treatment (table IV). In the few patients who received endocrine treatment alone

partial response was observed in four out of 15 controls (median duration 16 months) and three out of 22 patients in the CMF group (median duration 7.5 months).

EARLY AND LATE TOXICITY

The incidence of acute toxic reactions have been reported.⁵⁻⁶ Nausea, vomiting, and hair loss were the most distressing effects. In no patient did haematological or infectious complications occur from repeated episodes of myelosuppression, and no evidence of liver damage attributable to prolonged administration of methotrexate was detected.¹³ The incidences of second neoplasms were comparable between the two groups. Contralateral breast cancer was discovered in four controls and six of the CMF-treated patients. In one patient in the CMF group the histological type was cystosarcoma phylloides. New solid tumours in other organs were detected in five patients (three controls, two in the CMF group), whereas no cases of acute leukaemia occurred.

Five patients (two controls, three in the CMF group) died without clinical evidence of disease. The two control women (aged 71 and 73 years) died of cerebrovascular accident and head injury, respectively, 57 and 36 months after operation. The clinical causes of death of the other three patients were cerebrovascular accident in two and heart failure in the third. These patients were aged 59, 70, and 71 years and died 28, 31, and 61 months after mastectomy, respectively.

Discussion

This study of women with operable breast cancer showed significantly improved overall results at five years in the group given CMF after operation. Hence several biological and practical factors must be considered. The first is the observation that CMF chemotherapy, which produces an objective response (usually partial) in 50-55% of women with overt metastatic breast cancer,⁹⁻¹⁴ can exert a therapeutic effect on micro-metastases that may last for at least five years. Thus laboratory findings³ that neoplastic cells may be more vulnerable to the same cytotoxic drugs in more favourable kinetic conditions—that is, minimal residual disease—are confirmed clinically in an important solid tumour such as primary breast cancer with metastases in axillary lymph nodes. The variations in outcome with different degrees of axillary nodal disease probably further support the laboratory findings.

A second consideration concerns another important correlation between laboratory and clinical data. As in a separate, larger series of CMF-treated patients,¹³ we observed a dose-response effect of adjuvant chemotherapy. Regardless of menopausal state, clinical benefit increased with the amount of drug administered and was significant for patients receiving nearly the full dose. In contrast, patients given low-dose chemotherapy showed relapse-free survival rates similar to those of the controls. We recently confirmed the important role of drug dosage in a two-year, prospective randomised trial of two dose schedules of adjuvant chemotherapy in postmenopausal women. Relapse-free survival was significantly inferior in the group beginning with low-dose (<65%) CMFP (cyclophosphamide, methotrexate, fluorouracil, prednisone) compared with that of patients given the full dose regimen from the first treatment cycle.¹⁵ All these findings confirm that the outcome of combined treatment depend on the adequacy of both treatment modalities (local and regional, and systemic).

A third consideration concerns untoward effects of adjuvant chemotherapy. Our findings suggest that the incidence and degree of early as well as late toxicity are acceptable. Aside from frequent vomiting after each injection of methotrexate and fluorouracil, gastric disturbance while receiving oral cyclophosphamide was probably the most consistent side effect. Frank alopecia and haemorrhagic cystitis were rare.^{5,6} While myelosuppression and chemical cystitis were dose-limiting factors in all age groups, all toxic manifestations but amenorrhoea

in late premenopausal women were reversible. In our series late toxicity such as chronic organ damage and increased incidence of second neoplasms was not observed. Longer follow-up will, however, be needed to assess the true incidence of late morbidity. Some psychological and socioeconomic problems resulting from prolonged adjuvant chemotherapy were recognised during the study but were not quantitatively defined. Overall our results in terms of relapse-free survival and total survival appeared to outweigh the disadvantages of early toxicity and psychological and financial difficulties.

In conclusion the five-year results of our first adjuvant CMF programme have shown the efficacy of a multimodal approach in a high-risk group with resectable mammary carcinoma. More work is required, however, and other studies¹⁸⁻²¹ have examined the value of adjuvant chemotherapy in relation to critical variables such as menopausal state. Clinical investigation continues to be indicated, and studies are in progress testing hormonal manipulation alone or with chemotherapy, the role of immune stimulation, the effect of chemotherapy in high-risk groups of women with tumours not affecting axillary lymph nodes, and non-cross-resistant regimens. As a result of multi-centre studies future analyses, by critically reconsidering prognostic variables, will better define the subgroups who can most benefit from adjuvant therapy and provide more-detailed information on type and duration of treatment for given variables.

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References

- Valagussa P, Bonadonna G, Veronesi U. Patterns of relapse and survival following radical mastectomy. Analysis of 716 consecutive patients. *Cancer* 1978;**41**:1170-8.
- Fisher B. Biological and clinical considerations regarding the use of surgery and chemotherapy in the treatment of primary breast cancer. *Cancer* 1977;**40**:574-87.
- Schabel FM. Rationale for adjuvant chemotherapy. *Cancer* 1977;**39**:2875-82.
- Tormey DC. Combined chemotherapy and surgery in breast cancer: a review. *Cancer* 1975;**36**:881-92.
- Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med* 1976;**294**:405-10.
- Bonadonna G, Rossi A, Valagussa P, Banfi A, Veronesi U. The CMF program for operable breast cancer with positive axillary nodes. Updated analysis on the disease-free interval, site of relapse and drug tolerance. *Cancer* 1977;**39**:2904-15.
- Rossi A, Bonadonna G, Tancini G, et al. Trials of adjuvant chemotherapy in breast cancer. The experience of the Istituto Nazionale Tumori di Milan. In: Mouridsen HT, Palshof T, eds. *Breast cancer. Experimental and clinical aspects*. Oxford: Pergamon Press, 1980:149-56.
- Henney JE, De Vita VT Jr. The evolution of primary multimodality treatment in resectable breast cancer. *Cancer* 1980;**46**:999-1008.
- Carter SK. Surgery plus adjuvant chemotherapy. A review of therapeutic implications. I. Breast cancer. *Cancer Chemother Pharmacol* 1980;**4**:147-63.
- Brambilla C, De Lena M, Rossi A, Valagussa P, Bonadonna G. Response and survival in advanced breast cancer after two non-cross-resistant combinations. *Br Med J* 1976;**ii**:801-4.
- Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977;**35**:1-39.
- Bonadonna G, Valagussa P. Dose-response effect after CMF chemotherapy in breast cancer. *N Engl J Med* 1981;**304**:10-5.
- Bajetta E, Buzzoni R, Giardini R, Bonadonna G. Liver damage in women receiving adjuvant CMF chemotherapy. *Tumori* (in press).
- Canellios GP, Pocock SJ, Taylor SG III, Sears ME, Klaasen DJ, Band PR. Combination chemotherapy for metastatic breast cancer: prospective comparison of multiple drug chemotherapy with L-phenylalanine mustard. *Cancer* 1976;**38**:1882-6.
- Brambilla C, Valagussa P, Bonadonna G, Veronesi U. Sequential adjuvant chemotherapy in postmenopausal (<65 yrs) breast cancer. *Proceedings of the American Association for Cancer Research* 1980;**21**:189.

- ¹⁶ Ahmann DL, Payne WS, Scanlon PW, *et al.* Repeated adjuvant chemotherapy with phenylalanine mustard or 5-fluorouracil, cyclophosphamide, and prednisone with or without radiation, after mastectomy for breast cancer. *Lancet* 1978;ii:893-6.
- ¹⁷ Buzdar AU, Blumenschein GR, Gutterman JU, *et al.* Postoperative adjuvant chemotherapy with 5-fluorouracil, adriamycin, cyclophosphamide and BCG. A follow-up report. *JAMA* 1979;242:1509-13.
- ¹⁸ Wendt AG, Jones SE, Salmon SE, *et al.* Adjuvant treatment of breast cancer with adriamycin-cyclophosphamide with or without radiation therapy. In: Salmon SE, Jones SE, eds. *Adjuvant therapy of cancer II*. New York: Grune and Stratton, 1979:285-93.

- ¹⁹ Weiss R, Tormey DC, Glidewell O, *et al.* Evaluation of postoperative chemioimmunotherapy in mammary carcinoma. *Proceedings of the American Association for Cancer Research* 1979;20:244.
- ²⁰ Fisher B, Redmond C, Fisher ER. The contribution of recent NSABP clinical trials of primary breast cancer therapy to an understanding of tumor biology. An overview of findings. *Cancer* 1980;46:1009-25.
- ²¹ Forastiere AA, Hakes TB, Tallos P, *et al.* CMF±levamisole (L) breast adjuvant chemotherapy: analysis of results after 3-5 years. *Proceedings of the American Society of Clinical Oncology* 1980;21:402.

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SHORT REPORTS

Intramuscular cimetidine is safe and acceptable

Cimetidine is available as tablets, a syrup, or a preparation for intravenous injection, but in some patients administration by the intramuscular route is desirable. We therefore studied the safety and acceptability of intramuscular injection of cimetidine.

Patients, methods, and results

We studied 27 men and 11 women aged 22-79 (median 65.5) years. Twenty-five had duodenal or gastric ulceration, five oesophagitis, two duodenitis, two dyspepsia, and one each gastric erosions, bleeding oesophageal varices, a deformed duodenal bulb, and pruritus. All were inpatients already receiving oral cimetidine 200 mg thrice daily plus 400 mg at night.

Nineteen patients were studied in a double-blind cross-over trial. On the first day the midday dose of cimetidine was replaced by either intramuscular cimetidine 200 mg and a placebo tablet, or a placebo injection and cimetidine 200 mg by mouth. The next day the alternative treatment was given, the order being randomised. The two injections were given into opposite buttocks. Blood samples for creatine kinase activity were taken immediately before, and 24 hours after, each injection. Pain at the injection site was assessed as none, mild, moderate, or severe 10 minutes and six hours after each injection, and at the same time the site was inspected for any local reaction. The remaining 19 patients received intramuscular cimetidine 200 mg six hourly for 24 hours, oral cimetidine being omitted. Each injection site was numbered serially, and two to four hours after the last injection the appearance of each site was noted.

The cimetidine injection (200 mg in 2 ml) for intramuscular use was the same formulation as the standard intravenous preparation. The placebo injection was 2 ml 0.9% sodium chloride. All injections were given by trained nursing staff. Written informed consent was obtained from each patient, and the study had the approval of the hospital ethical committee.

After a single intramuscular injection of cimetidine one patient reported mild pain at 10 minutes that had resolved by six hours and another had moderate pain at six hours that had disappeared by the next day. After placebo injection two other patients reported mild pain at six hours but none had pain at 10 minutes. The injection sites appeared normal except after a placebo injection in one patient, who had erythema at 10 minutes that had resolved by six hours. Serum creatine kinase activity remained normal after all injections. One patient felt light-headed transiently after injection of cimetidine, while another complained of aching in the buttock for a few hours after both injections.

Of the 19 patients receiving intramuscular cimetidine six hourly, 14 had no reaction at any of the injection sites. One patient had erythema with some swelling at one site and erythema alone at another site. The remaining four patients had erythema at one injection site. No adverse events occurred and no patient had to be withdrawn from either part of the study.

Comment

Our study showed that reactions at the injection site were uncommon and as likely with placebo as with intramuscular cimetidine. Though parenteral cimetidine may be overused by hospital doctors,¹ oral medication cannot be given to patients with an ileus or persistent vomiting. Because of occasional reports of hypotension² and cardiac arrhythmias³ after intravenous cimetidine many hospitals do not allow nurses to give the drug by this route.

Peak plasma concentrations after intramuscular cimetidine are 30-

50% of those achieved after similar intravenous doses, and there is no significant difference in bioavailability (D Rowley-Jones, personal communication). Intramuscular administration of cimetidine is therefore a convenient and safe alternative to intravenous administration when the parenteral route is indicated.

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¹ Brater DC, Toney F. Misuse of cimetidine. *N Engl J Med* 1980;303:702.

² Mahon WA, Kolton M. Hypotension after intravenous cimetidine. *Lancet* 1978;ii:828.

³ Cohen J, Weetman AP, Dargie HJ, Krikler DM. Life-threatening arrhythmias and intravenous cimetidine. *Br Med J* 1979;iii:768.

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Familial colorectal cancer and hereditary brachydactyly

Soft-tissue and skeletal abnormalities are associated with colorectal cancer in Gardner's, Turcot's, and Peutz-Jeghers's syndromes. Detailed radiological studies have shown osteomas in most patients with familial polyposis coli.¹ Osteomas and fibromas may also be associated with colorectal cancer in the absence of multiple polyposis.² To our knowledge the only other reported skeletal abnormality associated with colorectal cancer is the nail-patella syndrome.³ We describe a family with hereditary brachydactyly associated with colorectal cancer.

Family study

The brachydactyly consisted of hypoplasia of the second, third, and fifth middle phalanges of both hands (figure), the severity of the condition varying among family members. In some cases the hypoplasia was restricted to the fifth finger, whereas in others the fourth and fifth metacarpals were also affected. One subject had changes in the segmental ratios of phalanges and metatarsals in both feet.

Brachydactyly had been present in five out of seven siblings. Three of the five had died of colorectal cancer, and the other two had died of unrelated disorders at 29 and 68 years of age. One of the two siblings without hand