Significance of a fall in serum CEA concentration in patients treated with cytotoxic chemotherapy for disseminated colorectal cancer

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SUMMARY 'Tumour response', defined as clinical or radiological evidence of tumour shrinkage is frequently regarded as an objective of chemotherapy, rather than as a predictor of prolonged survival. This study has assessed whether a fall in the serum CEA concentration after chemotherapy for disseminated colorectal cancer is a predictor of prolonged survival and compared it with tumour response as a predictor of survival. There was a 37% improvement in median survival among patients whose serum CEA concentration fell after chemotherapy (70% of patients treated) compared with patients whose serum CEA did not fall. The use of >25% clinical or radiological tumour shrinkage as a predictor of prolonged survival identified a smaller proportion (36%) of patients in whom there was a 52% prolongation in median survival compared with patients whose tumours shrank less than 25%, or did not shrink. Proportional hazards regression analysis suggested that tumour shrinkage was a stronger predictor of survival. A fall in serum CEA concentration, however, identified a group of patients whose tumours did not shrink, but who had a 27% improvement in median survival compared with those whose tumours did not shrink and whose serum CEA concentration did not fall. Monitoring of the serum CEA during the first two months of treatment appears to provide a sensitive and economical means of identifying those patients whose survival is likely to be prolonged by chemotherapy for colorectal cancer.

The value of serum carcinoembryonic antigen (CEA) monitoring in the detection of recurrent colorectal cancer has been established.¹ Some patients with recurrent disease can be treated by a second surgical resection but for most, cytotoxic chemotherapy offers the only chance of slowing the progress of the disease. The potential benefits of effective chemotherapy are a prolongation of survival and an improvement in performance status.

It would be useful to establish criteria which could identify early, those patients whose survival will be prolonged by chemotherapy. It is generally assumed that clinical or radiological evidence of tumour shrinkage, referred to as response, is associated with

prolongation of survival. Among patients with serum CEA producing tumours, a change in the level of serum CEA may reflect a change in the burden of disease. Thus, a reduction in the serum CEA concentration after chemotherapy might also predict prolonged survival, as has been suggested in a study of 36 patients by Hine and Dykes.²

The objective of this study was to determine whether a fall in serum CEA after chemotherapy was associated with prolonged survival in a population of over 300 patients treated with chemotherapy for disseminated colorectal cancer.

Methods

PATIENTS

The population under study consisted of 329 patients with metastatic colorectal carcinoma, who received

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chemotherapy at Memorial Sloan-Kettering Cancer Center (MSKCC) within the period 1976 to 1984. Two hundred and sixty five patients received systemic chemotherapy: 137 received methylCCNU, 5-fluorouracil, vincristine and streptozotocin (MOF-Strep); 22 received methotrexate and 5-fluorouracil; and 106 received methylCCNU, vincristine and 5-fluorouracil (MOF). Sixty four patients received hepatic infusional therapy with fluorodeoxyuridine (FUDR).

Response was defined in the following manner: a partial response (PR) was a >50% reduction in the sum of the perpendicular axes of the tumour, measured radiologically for at least four weeks; a minor response (MR) denoted a >25% but <50% tumour reduction of measurable disease; stable disease was defined as no growth in tumour size for at least two months. Two serum CEA measurements were used, an initial value and the nadir which usually occurred within two months after the start of chemotherapy. A fall in serum CEA was defined as any reduction below the pretreatment serum CEA level. To allow for measurement error a more stringent definition of CEA fall as >10% fall from baseline was also considered. All serum CEA measurements were done in the same laboratory, by an indirect method using Hansen's assay.³ Karnofsky performance status (KPS), serum lactic dehydrogenase (LDH), alkaline phosphatase (alk phos), and white blood count (WBC) were measured in all patients before treatment.

STATISTICAL ANALYSIS

Survival was measured from the time of protocol entry until death or last follow up. The survival distributions for different groups of patients were estimated using the Kaplan-Meier, or product limit method⁴ and then compared by the logrank test.⁵ Confidence limits (CL) for median survival times were determined using the method proposed by Simon and Lee.⁶ A consideration in these analyses was length bias because the chance of a patient being classified as a responder is influenced by the length of survival. As this study was retrospective in nature, the 'landmark method' of adjusting for length bias could not be used.⁷ To reduce the effect of length bias in survival analyses involving tumour shrinkage and change in CEA, patients who died within the first two months of receiving chemotherapy were omitted from the survival analyses. Thus there was a total of 290 patients in the sample (88% of total).

The relative importance of several predictors of survival was assessed by stepwise proportional hazards regression analysis.⁸ The variables in the model were: CEA decrease v CEA increase or no change in CEA; response v no response; LDH <229

U/l v LDH 230-500 U/l v LDH >500 U/l; WBC <10000 cells mm³ v WBC > 10000 cells mm³; alk phos <115 U/l v alk phos >115 U/l; KPS <70 v KPS >70; route of chemotherapy administration, regional v systemic infusion.

The initial serum CEA concentrations in patients whose CEA decreased were compared with those in patients whose CEA remained the same or increased using Student's *t* test. To control for variation in serum CEA concentrations, the natural logs of the serum CEA were taken when making comparisons.

Results

TUMOUR SHRINKAGE AS A PREDICTOR OF SURVIVAL

One hundred and nine patients had a tumour response which was classified as a PR or MR. The median survival of these patients was 13.7 months (95% CL 12.0-17.7 months) which was significantly ($p<0.00001$) better than the median survival of nine months (CL 8.2-10.5 months) in the remaining patients who did not have a documented response (Fig. 1).

CHANGE IN SERUM CEA CONCENTRATION AS A PREDICTOR OF SURVIVAL

The serum CEA fell in 70% of patients usually within two months of starting chemotherapy. Sixty two per

Fig. 1 There was a significant ($p<0.00001$) improvement in the survival of patients whose tumours decreased >25% after chemotherapy (□) compared with patients whose tumours decreased by <25% or did not change (X).

cent of these patients in whom the serum CEA fell experienced a fall of $>20\%$ of the initial serum CEA value. The serum CEA remained stable or continued to rise in the remaining 30% of the patients. Among the patients in whom the serum CEA fell after chemotherapy median survival was 12 months (CL 11.0-13.7 months) which was significantly ($p=0.0002$) longer than a median survival of 8.8 months (CL 6.7-10.5 months) for those with no fall in serum CEA (Fig. 2). Allowing for an error in the measurement of serum CEA decrease, patients in whom serum CEA fell $>10\%$ from baseline after chemotherapy were compared with those with no fall, stable values or a $<10\%$ fall. Those with a $>10\%$ fall in CEA had a significantly longer survival ($p=0.0002$). There was no significant difference between the two groups in the pretreatment serum CEA level. The geometric means of the natural logarithms of pretreatment serum CEA were compared because of large variability in the raw values (a mean of 495.9 ± 1677 and 432.68 ± 3493 , for patients with no serum CEA fall *versus* those with a CEA fall, respectively). The numbers of patients receiving each treatment regimen were comparably distributed between those patients experiencing a fall in CEA and those who did not ($p=0.16$).

RELATIONSHIP BETWEEN CHANGE IN SERUM CEA CONCENTRATION AND SURVIVAL AMONG NON-RESPONDERS

Among the 175 patients who did not show a documented tumour response, patients who had a serum

Fig. 2 There was a significant ($p<0.0002$) improvement in the survival of patients whose serum CEA concentration fell after chemotherapy (□) compared with patients in whom CEA did not fall (X).

Fig. 3 Among patients in whom tumour shrinkage of $>25\%$ did not occur (non-responders) there was a significant ($p=0.04$) improvement in survival among those in whom the serum CEA concentration fell (□) compared with those in whom CEA did not fall (X).

CEA decrease experienced significantly ($p=0.04$) longer survival than patients whose CEA rose or remained the same (Fig. 3). The estimated median survival in non-responders whose serum CEA fell was 10.2 months (CL 9.0-12.0 months) *versus* 8.0 months (CL 6.1-9.0 months) for the remaining non-responders with no fall in serum CEA.

Univariate survival analyses indicated that KPS, LDH, alk phos, and type of treatment were significantly related to survival (Table 1). Alkaline phosphatase, however, was not included in the final model because it was not significant in the multivariate analysis. Allowing for initial KPS, serum LDH and type of treatment, a fall in the serum CEA remained a significant predictor of improved survival (improvement χ^2 $p=0.001$). In addition a fall in serum CEA remained predictive of survival even when eventual response status was considered in the analysis (improvement χ^2 $p=0.008$).

STABLE DISEASE SUBGROUP

In sixty three patients the serum CEA concentration did not increase or decrease more than 20% from pretreatment baseline. There was no significant difference ($p=0.4$) between the survival curves of patients whose CEA concentration fell by $<20\%$, median survival 12.0 months (CL 6.0–11.5 months) compared with patients whose CEA level rose by $<20\%$ or remained the same, median survival 8.6 months (CL 6.0–11.5 months). With this sample size the power to detect a difference is 60%.

Table 1 Pretreatment factors which were shown on univariate analysis to influence survival

Variable	Value
Karnofsky performance status	<0.00001
Serum lactic dehydrogenase	<0.00001
Alkaline phosphatase	0.00001
Type of treatment	0.001

Discussion

Predictors of improved survival resulting from chemotherapy can be viewed as a continuum from the most rigorous – that is, complete tumour disappearance, through varying degrees of tumour shrinkage, to a fall in the serum CEA concentration without tumour shrinkage. Thus response as defined by tumour shrinkage is a more stringent criterion than response as defined by a fall in the serum CEA concentration and may predict a different enhancement in survival. For this reason when comparing chemotherapy studies, a fall in the serum CEA concentration should not be equated with other criteria of response. Previous studies (Table 2), treating tumour shrinkage as an objective or endpoint of treatment, have suggested that a decrease in serum CEA is a poor predictor of tumour shrinkage because while it is sensitive (low false negative) it is also non-specific (high false positive).

Rather than regarding tumour shrinkage as an objective of treatment, another approach is to consider survival as the endpoint of analysis and to seek to identify predictors of improved survival arising from chemotherapy. The results of our study indicate that a fall in the serum CEA concentration after chemotherapy, although not an accurate reflection of eventual tumour shrinkage, did identify patients whose survival was enhanced by chemotherapy. The estimated median survival for patients who experienced a fall in serum CEA was 12.0 months. If this group was characterised further as those experiencing a CEA reduction of <20%,

21–49% or >50%, the median survivals were 12.0, 10.4 and 12.9 months, respectively. This suggests that a fall in the serum CEA was more important than the size of the fall. This survival benefit occurred even when favourable pretreatment prognostic indicators such as high performance status and low LDH level were considered. Moreover, knowledge of serum CEA change provided additional information about survival when the eventual degree of tumour shrinkage was known. Thus, there was a component of change in serum CEA which related to survival and was not attributable to either pretreatment predictors¹⁴ or to the propensity of the tumour to shrink after chemotherapy.

It has been suggested¹⁵ that, because of daily fluctuations in the serum CEA concentration, patients whose serum CEA remains within $\pm 32\%$ of the previous baseline level form a homogenous subgroup who have stable disease. In our patients, the estimated median survival for patients whose CEA increased by 20% was less than the median survival for patients whose serum CEA fell by 20%. As the power of this analysis was only 60%, differences were not easily detectable; however, the estimated median survival times (12 and 8.6 months, respectively) were not clearly supportive of a homogenous subgroup of patients. In this study, where the serum CEA was measured before treatment and during the first two months of treatment, day to day fluctuations in serum CEA did not seem to obscure the improved survival associated with even a small (>10%) fall in serum CEA.

The important consideration resulting from this investigation is that knowledge of a change in serum CEA concentration may be useful as an indicator of survival after chemotherapy. Both tumour shrinkage and reduction in serum CEA concentration appear to be useful in predicting prolonged survival in patients receiving cancer chemotherapy. Monitoring serum CEA values during treatment may be the more economical means of identifying those patients whose survival is likely to be prolonged by chemotherapy.

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Table 2 Relationship between tumour responses and fall in CEA. A fall in serum CEA frequently occurs in the absence (false +ve) of response – defined as tumour shrinkage

Reference	n	Response %	Prediction of response by CEA test	
			False +	False –
10	93	10	17/26 (65%)	0/67 (0%)
11	122	25	19/33 (57%)	17/98 (19%)
12	24	17	4/8 (50%)	0/16 (0%)
13	49	37	4/20 (20%)	2/29 (7%)
Total	288	22%	44/87 (51%)	19/201 (9%)

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