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MONITORING PALLIATIVE CHEMOTHERAPY IN ADVANCED GASTROINTESTINAL CANCER USING SERIAL TISSUE POLYPEPTIDE SPECIFIC ANTIGEN (TPS) MEASUREMENTS

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Tissue polypeptide antigen specific (TPS) was analysed in serum taken prior to chemotherapy in 90 patients with advanced gastrointestinal cancer and prior to every treatment course in 68 of these patients in order to explore whether serial tumour marker measurements can be of importance in monitoring patients treated with palliative chemotherapy. Elevated TPS levels were seen in 83/90 (92%) patients (48/52 colorectal, 9/9 pancreatic, 9/11 biliary, 17/18 gastric). Baseline TPS level correlated with performance status, tumour response and survival. Based upon the change in TPS levels after the first two courses in relation to baseline, a decrease by >50% had a high sensitivity for a favourable treatment outcome (partial remission and prolonged stationary disease (90%) or a subjective response (100%)), whereas the specificity was lower (72% and 73% respectively). A similar result was seen when the TPS levels were analysed at the time of the response evaluation after 2 months (sensitivity 91 and 95%, specificity 74 and 75% for an objective or subjective response respectively). In 7 out of 15 patients with an initially favourable outcome, an increase in TPS levels of >50% at two occasions was seen 8–20 weeks prior to clinical disease progression. In advanced gastrointestinal cancer serial TPS measurements can with high accuracy early identify patients who will not benefit from the treatment. On the other hand, a response must be confirmed using other methods in the presence of a decrease, since this was also seen in non-responding patients.

Chemotherapy is widely used for palliation in advanced gastrointestinal cancer. The objectives are to relieve tumour-related symptons, prolong a symptom-free period and possibly to prolong survival without being too detrimental to overall well-being. However, only a proportion of the patients in whom treatment is initiated will benefit. Thus, better predictors for a favourable treatment outcome are desirable. Although the proportion of responders is limited, several patients demand active treatment (1). Early identification of non-responders would be valuable in order to save the patients from further treatment-associated toxicity and to reduce costs for the society. Further, also in patients initially responding, the disease will ultimately progress, and, likewise, in order to save toxicity and costs, the time point for maximal response would be desirable to identify as early as possible.

A number of clinical and laboratory parameters have been shown to predict tumour response (2–5). Apart from ruling out the poorest patients with very low probability to respond, none of these studies have yielded practically important findings in patient selection. Also, very few of the prognostic models have been validated on an independent material (6).

Response to palliative chemotherapy is usually performed by serial imaging. Therefore, it usually takes 2 or 3 months before any response can be evaluated. Symptom relief may be achieved more rapidly, but the reliability of

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early symptom relief as an indicator of response has not been systematically investigated. A simple and inexpensive method to monitor treatment response would be repeated measurements of tumour markers. A few studies have indicated that a decrease in tumour marker level has a low false negative rate but a high false positive rate as a predictor of tumour response (7–9). The tumour marker carcinoembryonic antigen (CEA) has been most extensively studied, although other tumour markers have been investigated and found to yield similar results (9, 10). The role of serial tumour marker measurements in clinical practice has not yet been settled.

To further explore the potential value of serial tumour marker assessments for response evaluation in advanced gastrintestinal cancer patients, a study using tissue polypeptide specific antigen (TPS) was performed. TPS reactivity is derived from specific epitopes of the c-terminal part of human cytokeratin 18 (11, Rydlander et al. Beki AB, Stockholm, Sweden, pers. commun.). TPS was selected since it has been claimed that it not only reflects tumour burden but also tumour cell activity (12). The study was primarily designed to answer the following question: 1) Can TPS measurements as early as after the first or second treatment course, i.e. usually within a month, indicate tumour response?, 2) Can pretreatment TPS-levels predict treatment outcome and survival?, 3) Can TPS measurements at the time of the first response evaluation substitute the radiologic examination?, and 4) Can a rise in TPS levels in responding patients predict progression before it is evident radiologically or clinically?

Material and Methods

Patients and treatment

Between November 1992 and October 1994, 90 consecutive patients with advanced gastrointestinal carcinoma were seen at the Department of Oncology, Akademiska sjukhuset, Uppsala. Fifty-two patients had colorectal cancer, 9 pancreatic cancer, 11 biliary cancer and 18 gastric cancer. Fifty-one patients were males and 39 females, the median age was 64 (range 30–80) years. The median follow-up of living patients was 7 months (range 4–26 months). All patients were evalauted for participation in ongoing chemotherapy studies. Colorectal cancer patients were treated with sequential 5-fluorouracil (5-FU)/leucovorin (FLv, 13) where 5-FU was given either as a bolus injection during 3 min or as a short-term infusion during 15 min (14). Treatment courses were repeated every 14 days. Patients with gastric, pancreatic or biliary cancer were randomized between immediate chemotherapy plus best supportive care or best supportive care where delayed chemotherapy was allowed (15). Gastric cancer patients were treated with etoposide, leucovorin, 5-FU (ELF, 15), and pancreatic and biliary cancer patients with 5-FU 500 mg/m^2 bolus i.v., etoposide 120 mg/m^2 for 40 min and leucovorin 60 mg/m^2 bolus i.v. (FELv). The treatment was repeated three consecutive days every third week. Elderly patients were treated with FLv insead of ELF or FELv.

Serum sampling

Serum was obtained from all patients before chemotherapy. Subsequent sampling was performed prior to all treatment courses, i.e. with an interval of 2 or 3 weeks according to regimens. The serum samples were aliquoted and immediately frozen at −20°C and stored until assayed.

Assessment of tumour response

Objective and subjective tumour response evaluations were performed according to study protocols every second month, i.e. after every fourth FLv treatment or every third ELF or FELv treatment. Objective tumour response was assessed according to standard criteria (17). A complete (CR) or partial (PR) response and stationary disease (SD) had to be present at two consecutive evalautions, i.e. with a minimum duration of four months. Patients who had stationary disease after 2 months and then progressed were designated SD/PD. In all other instances, progressive disease (PD) was present. All assessments were done with CT-scanning and/or other radiography.

A subjective response evaluation was performed by the treating doctor at the same time as the objective response evaluation. This evaluation was based on a personal interview. A subjective response (designated improved) was present when the patient's symptomatology had improved for at least four months with no signs of severe adverse treatment effects. If a patient was improved after 2 months but then progressed, they were designated improved/worse whereas all other patients were worse. Both the objective and the subjective response evaluations and their durations were identical to those used in previous trials (13, 14, 18–20).

TPS measurements

TPS was measured by a solid phase, immunoradiometric assay (TPS^{TM} IRMA, BEKI Diagnostics AB, Bromma, Sweden). All samples were run in duplicate. The upper normal level of TPS in serum was defined as 80 U/l. The precision of the TPS-assay was 7% (intra- and interassay) according to the manufacturer. Any changes in TPS levels during treatment were expressed in percentage of the baseline value. The earliest TPS-response evaluation was based upon the value before the third treatment course (categorized into an increase by >25%, no change (±25%), a decrease between 25 and 50% and a decrease by >50%) provided that the level before the second course was not

Table 1

The sensitivity[a], specificity, positive and negative predictive values of serial TPS-measurements in evaluating a clinical response

	Initial evaluation		After 2 months	
	CR + PR + SD vs SD/PD + PD	Improved vs impr/worse + worse	CR + PR + SD vs SD/PD + PD	Improved vs impr/worse + worse
Sensitivity	19/21 (91)	19/19 (100)	20/22 (91)	19/20 (95)
Specificity	26/36 (72)	24/33 (73)	17/23 (74)	15/20 (75)
Positive predictive value	19/29 (66)	19/28 (68)	20/26 (77)	19/24 (79)
Negative predictive value	26/28 (93)	24/24 (100)	17/19 (90)	15/16 (94)

[a] Sensitivity = true positive (decrease in a patient with response)/true positive + false negative (no decrease in a patient with response); specificity = true negative (no decrease if no response)/true negative + false positive (decrease in a patient with no response); positive predictive value = true positive/true positive + false positive; negative predictive value = true negative/true negative + false negative. The calculations were based upon change in TPS-values > −50%.

>25% lower; if so, an increase was present. The subsequent TPS-response evaluation was based upon the value taken in connection with the first response evaluation after 2 months. In patients with a normal baseline TPS, no calculations of a decrease were performed.

Statistical analyses

Comparisons of proportions between groups were performed with χ^2-analyses. Survival curves were constructed according to the life-table method and the log-rank test was used for testing differences (21). Correlations were studied with the Spearman's rank correlation test. The proportional hazards model was used to evaluate the importance of prognostic variables one by one and altogether (22). Comparison of changes in TPS levels in relation to objective, subjective responses were expressed in terms of sensitivity, specificity and positive and negative predictive value according to conventional definitions (see Table 1).

Results

Baseline TPS values

At baseline, pathologically elevated TPS levels occurred in all patients with pancreatic cancer, in all but one patient with gastric cancer and all but two patients with biliary cancer, whereas all but four patients with colorectal cancer had elevated levels (Fig. 1). Patients with normal baseline TPS levels had no or very minor tumour-related symptoms and were in good performance, i.e. Karnofsky performance status (KPS) 90–100, whereas the majority of the other patients were symptomatic and often had poor performance (KPS 50–80, median 70). There was an inverse correlation between the TPS level and KPS ($r = -0.37$, $p < 0.001$). In 19 patients, 2 analyses were performed prior to the first chemotherapy injection with an interval of 4–31 (median 15) days. In 10 of these patients, an increase of >25% (range 35–95%) was seen, and in the remaining 9 no change (±25%).

In the group of patients with measureable disease, 13 patients had CR + PR, 12 SD, 14 SD/PD, and 28 PD (Table 2). A subjective response in symptomatic patients was seen in 20 patients, a short-lived improvement in 4 and no improvement in 29 patients. The relations between an objective and a subjective resonse are illustrated in Table 2. Although more responses were seen in patients with colorectal and gastric cancer than in those with pancreatic and biliary cancer, the relations between a response and changes in TPS-levels were very similar, and separate data for the various tumour types are therefore not given.

There was a correlation between baseline TPS value and tumour response with CR + PR-rates of 32% (9/28) for those with TPS-values below 300 U/l, 18% (4/22) for those between 300–1 000 U/l and 0% (0/17) above 1 000 U/l

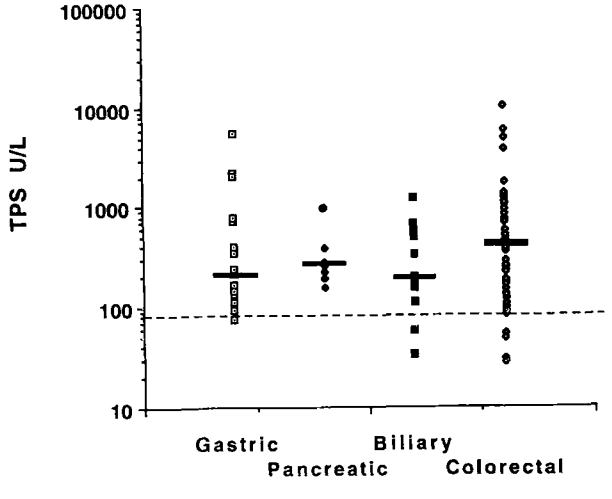

Fig. 1. Baseline TPS levels according to diagnosis. The upper normal TPS level is 80 U/l (– – –). Median TPS level is indicated by bars for each location.

Table 2

Relations between objective and subjective responses in patients treated with chemotherapy

Subjective response	Objective response					
	CR + PR	SD	SD/PD	PD	Not evaluable	All
	number of patients					
Improved	9	7	1		3	20
Improved/Worse			4			4
Worse			6	22	1	29
Not evaluable[a]	4	4	3	6	1	19
All	13	12	14	28	5	72

[a] These patients had no tumour-related symptoms prior to the start of treatment.

($p < 0.05$, χ^2-analysis). Three of the 17 patients with values above 1 000 U/l had SD. Baseline TPS value tended to correlate with a subjective response (11/20 [55%] below 300 U/l, 5/16 [31%] between 300 and 1 000 U/l, and 4/17 [24%] above 1 000 U/l, $p = 0.1$). There was no significant association between TPS level in continuous form and overall survival ($p = 0.12$). However, when TPS was analyzed in a dichotomized form, the median survival was 3 months in patients with a markedly elevated level (> 500 U/l) versus 8 months in those with a level of 500 or lower ($p < 0.01$, log-rank test, Fig. 2). Also KPS correlated strongly to survival ($p < 0.001$), whereas age and B-hemoglobin level did not ($p = 0.6$ and 0.2 respectively). KPS and B-hemoglobin level have in previous studies in advanced colorectal cancer given strong prognostic information (5, 6). When these three variables were tested together with TPS for influence on survival, only KPS retained its prognostic importance, i.e. TPS ($\gtrless 500$ U/l) lost its significance in the multivariate analysis (data not shown). This observation was also true when the analysis was restricted to colorectal cancer patients.

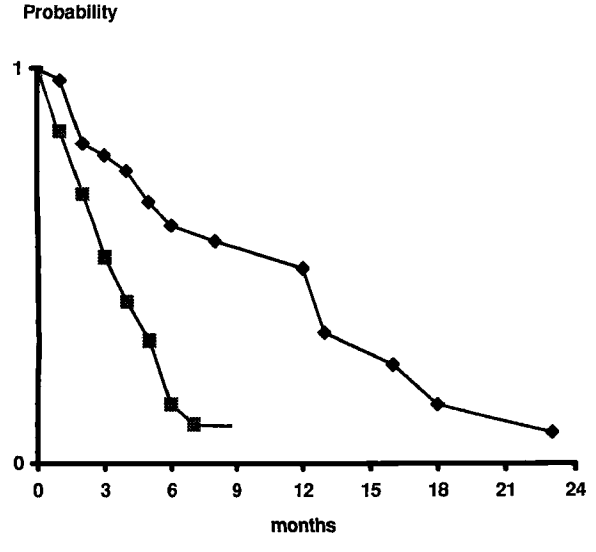

Fig. 2. Survival according to baseline TPS levels below ($n = 59$) or above ($n = 31$) 500 U/l respectively. This cut-off level yielded the highest χ^2-value when equality over strata tested with the log-rank test ($\chi^2 = 7.85$, $p < 0.01$). —◆— ≤ 500 U/l, —▣— > 500 U/l.

Early prediction of response

Serial TPS measurements were performed in 68 patients, all but one evaluable for objective response, subjective response or both. The change in TPS-levels during treatment for a patient is illustrated in Fig. 3. A decrease by at least 25% from baseline was seen in 48 (71%) patients before the second treatment course; in the remaining 20 patients either no change or an increase was seen. In 19 of these 20 patients, no later decrease was seen whereas in the

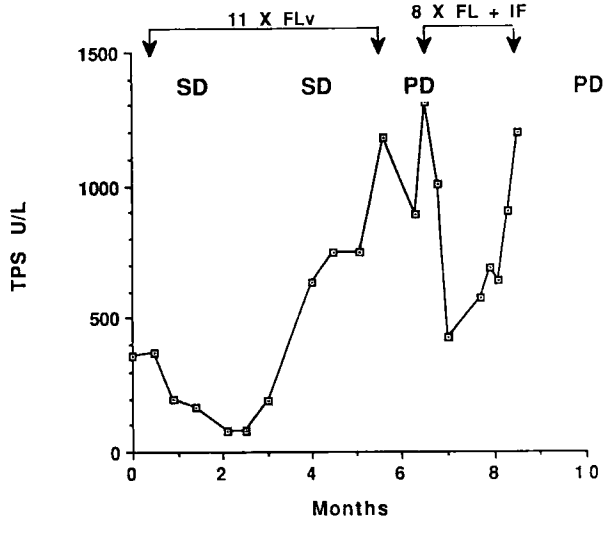

Fig. 3. TPS levels of a patient with colorectal cancer treated with FLv. The figure illustrates a slight increase in TPS level prior to treatment, the marked initial decrease during which time the patient had SD (a decrease not qualifying as PR was seen) and symptomatic improvement, and an increase several courses prior to PD was evident clinically and radiologically. A decrease of TPS levels was also seen when second-line treatment with 5-FU + leucovorin + interferon was initiated in spite of no response either objectively or subjectively.

Table 3

Prediction of response according to the initial change in TPS-values[a]

Change in TPS-values	Objective response				Subjective response		
	CR + PR	SD	SD/PD	PD	Improved	Improved/Worse	Worse
> +25%			2	7			8
±25%		1	1	11			12
(−)25–50%		1	1	4			4
> −50%	10	9	7	3	19	4	5

[a] The evaluation was based upon the level before the third treatment course in relation to baseline provided that the value before the second one was not even lower (>25%); if so, an increase (> +25%) was present. Patients with a normal baseline TPS value, within the reference range are not included.

patients with an initial decrease, the levels could continue to decrease for one or a few more courses, remain at a lower level for one or several courses or again increase. In practically all patients, the maximum decrease in TPS-levels had occurred already after the first two or three treatment courses. In 13 patients, the levels reached normal limits. The median number of courses (after the first one in the 48 patients with an initial decrease) before an increase by at least 25% from nadir was detectable was 3, range 1–20).

In all instances but one where the initial TPS-response after the first two treatment courses was categorized as an increase or no change, progressive disease was present (Table 3). All patients that later turned out to have CR + PR had a decrease in TPS levels by more than 50% during the first two treatment courses, and all patients but one with SD had a decrease by at least 25%. The exceptional patient had an initial decrease by 20–25% that then continued to decrease for several courses. An initial decrease by >50% was also seen in several patients having a short-lived stationary disease (SD/PD) and in three patients with PD. If the initial TPS evaluation had been based only upon the value prior to the third course not considering the value before the second course, 3 additional patients with PD had had a decrease by >50%. Sensitivity, specificity and predictive values for a clinical response (CR + PR + SD) are given in Table 1. If the analyses were restricted to patients with an objective response (CR + PR), the sensitivity was 100% (10/10) and the specificity 60% (28/47).

A marked initial decrease in TPS levels was also seen in all patients subjectively improved irrespective of whether this lasted for 2 or 4 months (Table 3). Again, some patients without any symptomatic improvement had a similar decrease in TPS levels. The sensitivity for a subjective response was thus 100%, whereas the specificity was lower (Table 1).

Prediction of response after two months

After two months of treatment, all patients with CR + PR and all but two with SD had a decrease in TPS levels by more than 50% compared to baseline (Table 4). Thus, the sensitivity for a clinical response (CR + PR + SD) was very high, whereas again the specificity was lower since several patients without a response (SD/PD + PD) had decreased TPS values (Tables 1 and 4). If only patients with CR + PR were included, the sensitivity was 100% (11/11) whereas the specificity was much lower (56%, 19/34). The same relations were also seen between the changes in TPS levels and a subjective tumour response (Tables 1 and 4).

Prediction of disease progression after an initial response

In 15 patients the treatment was continued, sometimes with prolonged intervals between the courses, until disease

Table 4

Prediction of response according to the TPS-value after 2 months of treatment in relation to baseline[a]

Change in TPS-values	Objective response				Subjective response		
	CR + PR	SD	SD/PD	PD	Improved	Improved/Worse	Worse
> +25%			1	6			6
±25%		1	5	4		1	6
(−)25–50%		1	1		1	1	1
> −50%	11	9	5	1	19	2	3

[a] Patients with a normal baseline TPS value are not included.

progression after an initially favourable outcome (CR + PR + SD and/or subjective improvement). In 7 of these patients, an increase of >50% of the lowest TPS level on two occasions was detected median 14 weeks (range 8–20) before disease progression was evident either as objective disease progression or worse symptomatology. In three patients, the increase was not detected until the progression was evident, and in five patients no such increase was seen in spite of progressive disease.

Discussion

In accordance with previous reports (23–26) elevated serum levels of TPS were found in a high proportion of patients with advanced gastrointestinal cancer. The TPS levels correlated in the present study with patient performance, thus indirectly indicating a correlation with tumour burden/tumour cell activity. The TPS levels also correlated with patient survival, and particularly clearly elevated levels indicated a poor prognosis. Furthermore, although not systematically investigated, repeated measurements in patients not treated with chemotherapy showed stable or increasing values, the latter most likely reflecting tumour cell growth. Thus, several findings in this study indicate that serial TPS measurements could be useful in monitoring this group of patients during treatment.

Baseline TPS levels above 1 000 U/l strongly indicated that the probability for an antitumoural effect was low or at most 20%. According to a Swedish consensus conference (27), this probability is too low for recommending palliative chemotherapy on a routine basis. In contrast, it the levels were below 1 000 U/l, the probability for a favourable response was above 30–40% with no clear difference between those with normal, slightly elevated or moderately elevated levels.

A striking finding in this study was a decrease in TPS levels in about 70% of the patients already after the first treatment course. The absence of an early decrease was in virtually all instances associated with an unfavourable tumour response, i.e. neither objective response, prolonged stabilisation nor subjective improvement. Also, if the initial decrease was followed by an increase after the second course, no response was seen. Thus, it can be claimed that the lack of any marked decrease after the first two treatment courses strongly indicate that the patient will not benefit from the treatment. This result thus suggests a clinical usefulness of serial TPS measurement that can save patients from further potentially toxic treatments.

The opposite conclusion, namely that a decrease in TPS-levels after the first one or two treatment courses demonstrates that the patient will favourable respond to the treatment is, however, not true. Actually, the specificity of the TPS decrease for tumour response, whether objective or subjective, was only 60–75%. The decrease in TPS levels most likely reflects tumour cell kill/decrease in tumour cell activity caused by the cytostatic drugs but that it in certain patients is not sufficiently large and/or durable to qualify as a response. Several patients classified as having progressive disease and who had decreased initial TPS levels experienced short-lived symptom improvements and in a few cases also transient tumour regression. A similar conclusion was also reached by Ward et al. (9) who reported decreasing CEA-levels also in patients with a minor tumour response. In order to qualify as a response, either objective or subjective, a minimum duration must be fulfilled according to internationally accepted criteria (17). We have in a series of studies (13, 14, 18–20) adopted a minimum duration of four months. This time period for objective responses is longer than generally perceived (28).

A tumour cell kill of such a magnitude that a complete remission is achieved is rarely seen in colorectal cancer, making up the largest group in this study. Partial remission using biochemically modified 5-FU are seen in between 20–25% and stable disease with a minimum duration of 4 months in another 20% (13, 18, 29). Thus, totally less than 50% of the patients have a measurable tumour effect. This figure is also true for a subjective response in symptomatic patients (14, 19). An initial decrease in the TPS levels in about 70% of the patients may indicate that the tumour cells are negatively influenced in more than half of the patients with advanced colorectal cancer. The benefit in terms of palliation or survival prolongation is, however, absent or at the most marginal in a proportion of these patients.

We have, similar to the results noticed in the present study, repeatedly found that not only an objective response (CR + PR) but also prolonged disease stabilization (SD) is associated with symptom relief and improved quality of life in practically all patients (14, 15, 20). In contrast, a more short-lived disease stabilization (SD/PD) is rarely of any palliative benefit (20). Both an objective response and a prolonged disease stabilization is most likely also associated with a survival prolongation in an individual patient (28). For these reasons, we believe that it is justified to include also patients with stationary disease, provided it has a minimum duration of 4 months from the start of therapy into the group of patients clinically responding to the treatment.

Measurement of the TPS levels at the time of the first response evaluation after two months of treatment may also be of practical importance. If the level had not decreased by at least 50% from baseline, the probability of a favourable response is very low, and the costs for radiology could be saved. On the other hand, if a decrease is present, any response must be confirmed, either radiologically or with adequate symptom/quality of life evaluation in a primarily symptomatic patient. Similar conclusions have been reached by others using CEA or other tumour markers (9, 10, 23, 30). In the study by Kornek et al. (23) including 39 patients followed with

serial measurements, TPS was found to yield superior predictive values to CEA and two other markers.

We also had the intention to explore whether an elevation in TPS levels during treatment could predict tumour progression earlier than it is detected clinically. Although comparably few patients were investigated in this way, our results indicate that this may be the case, but only in about half of the patients. It was also seen that the TPS levels during treatment in the absence of any evidence for tumour progression could fluctuate considerably in some patients. Therefore, strict criteria must be applied in order to consider increasing levels as an evidence for tumour progression.

In conclusion, this study has shown that TPS measurements before and during palliative chemotherapy for patients with advanced gastrointestinal cancer may be of practical importance and save toxicity for an individual patient and reduce costs for the society. Very high levels prior to treatment initiation indicate that the likelihood for a beneficial effect is low, although about 20% may still achieve a prolonged stabilization and/or symptom relief. A lack of any marked decrease in TPS levels already after the first two treatment courses strongly tells that treatment will not be beneficial, and it could be interrupted. Also the costs for imaging could be reduced in the absence of any decrease. A decrease does, however, overestimate the number of responses, and it must therefore be confirmed by other methods.

REFERENCES

1. Slevin ML, Slubbs L, Plant HJ, et al. Attitudes to chemotherapy: comparing views of patients with cancer with those of doctors, nurses, and general public. BMJ 1990; 300: 1458–60.
2. Lavin P, Mittelman A, Douglass H, et al. Survival and response to chemotherapy for advanced colorectal adenocarcinoma. An Eastern Cooperative Oncology Group Report. Cancer 1980; 46: 1536–43.
3. Kemeny N, Braun DW. Prognostic factors in advanced colorectal carcinoma. Importance of lactic dehydrogenas level, performance status and white blood cell count. Am J Med 1983; 74: 786–94.
4. Edler L, Heim ME, Quintero C, et al. Prognostic factors of advanced colorectal cancer patients. Eur J Cancer Clin Oncol 1986; 22: 1231–7.
5. Graf W, Glimelius B, Påhlman L. et al. Determinants of prognosis in advanced colorectal cancer patients treated with chemotherapy. Eur J Cancer 1991; 27: 1119–23.
6. Graf W, Påhlman L, Bergström R, et al. Appraisal of a model for prediction of prognosis in advanced colorectal cancer. Eur J Cancer 1994; 30: 453–7.
7. Allen-Mersh TG, Kemeny N, Niedzwiecki D, et al. Significance of a fall in serum CEA concentration in patients treated with cytotoxic chemotherapy for disseminated colorectal cancer. Gut 1986; 28: 1625–16.
8. Quentmeier A, Schlag P, Hohenberger P, et al. Assessment of serial carcinoembryonic antigen determinations to monitor the therapeutic progress and prognosis of metastatic liver disease treated by regional chemotherapy. J Surg Oncol 1989; 40: 112–8.
9. Ward U, Primrose JN, Finan PJ, et al. The use of tumour markers CEA, CA-195, and CA-242 in evaluating the response to chemotherapy in patients with advanced colorectal cancer. Br J Cancer 1993; 67: 1132–5.
10. Kuori M, Pyrhönen S, Kuusela P. Elevated CA19-9 as the most significant prognostic factor in advanced colorectal carcinoma. J Surg Oncol 1992; 49: 78–85.
11. Zetterberg A, Skern T, Schöber E, et al. Molecular characterization of TPS (Abstract). Tumor Biol 1995; 16: 334.
12. Björklund B. A conceptual approach to tumor antigen in the past and in the future with special reference to TPS. In: Ballesta AM, Torre GC, Bombardieri E, Gion M, Molina R, eds. Updating on tumor markers in tissues and in biological fluids. Torino: Minerva Medica 1993; 651–69.
13. Nordic Gastrointestinal Tumor Adjuvant Therapy Group. Biochemical modulation of 5-fluorouracil: A randomized comparison of sequential methotrexate, 5-fluorouracil and leucovorin versus sequential 5-fluorouracil and leucovorin in patients with advanced symptomatic colorectal cancer. Ann Oncol 1993; 4: 235–41.
14. Glimelius B, Hoffman K, Graf W, et al. Quality of life during chemotherapy in symptomatic patients with advanced colorectal cancer. Cancer 1994; 73: 556–62.
15. Glimelius B, Hoffman K, Haglund U, et al. Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. Ann Oncol 1994; 5: 189–90.
16. Wilke H, Pruesser P, Stahl M, et al. Etoposide, folinic acid, and 5-fluorouracil in carboplatin-pretreated patients with advanced gastric cancer. Cancer Chemother Pharmacol 1991; 29: 83–4.
17. Miller AB, Hoogstraten B, Staquet, et al. Reporting results of cancer treatment. Cancer 1981; 47: 207–14.
18. Nordic Gastrointestinal Tumour Adjuvant Therapy Group. Sequential methotrexate/5-fluorouracil/leucovorin (MFL) is superior to 5-fluorouracil alone in advanced symptomatic colorectal carcinoma: A randomized trial. J Clin Oncol 1989; 7: 1437–46.
19. Glimelius B, Hoffman K, Olafsdottir M, et al. Quality of life during cytostatic therapy for advanced symptomatic colorectal carcinoma: A randomized comparison of two regimens. Eur J Cancer Clin Oncol 1989; 25: 829–35.
20. Glimelius B, Graf W, Hoffman K, et al. General condition of asymptomatic patients with advanced colorectal cancer receiving palliative chemotherapy: A longitudinal study. Acta Oncol 1992; 31: 645–51.
21. 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.
22. Cox DR. Regression models and life tables. JR Stat Soc 1972; 34: 187–220.
23. Kornek G, Schenk T, Raderer M, et al. Tissue polypeptide specific antigen (TPS) in monitoring palliative treatment response of patients with gastrointestinal tumors. Br J Cancer 1995; 71: 182–5.
24. Lindmark G, Gerdin B, Påhlman L, et al. Prognostic predictors in colorectal cancer. Dis Colon Rectum 1994; 37: 1219–27.
25. Pasanen PA, Eskelinen M, Partanen K, et al. Diagnostic value of tissue polypeptide specific antigen in patients with pancreatic carcinoma. Tumour Biol 1994; 15: 52–60.
26. Slesak B, Harlozinska-Szmyrka A, Van Dalen A, et al. Tissue polypeptide antigen specific (TPS) and carcinoembryonic antigen (CEA) levels in cancerous and precancerous lesions in human colon. Oncology Reports 1995; 2: 567–70.

27. Consensus Statement. Cytostatic drug treatment in advanced cancer. MFR, Spri, Stockholm, Nov 1991.
28. Graf W, Glimelius B, Pählman L, et al. The relationship between an objective response to chemotherapy and survival in advanced colorectal cancer. Br J Cancer 1994; 70: 559–63.
29. Moertel CG. Chemotherapy for colorectal cancer. New Engl J Med 1994; 16: 1136–42.
30. Al-Sarraf M, Baker L, Talley R, et al. The value of serial carcinoembryonic antigen (CEA) in predicting response rate and survival of patients with gastrointestinal cancer treated with chemotherapy. Cancer 1979; 44: 1222–5.