Reflections on Treatment Strategies for Palliative Chemotherapy of Pancreatic Cancer

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Abstract. *Following our concept of efficacy-orientated sequential polychemotherapy, we report on the results of palliative chemotherapy in 69 patients suffering from exocrine pancreatic cancer, admitted to our unit in 2004. Evaluation of tumor response was mainly based on the serum courses of the tumor markers CA 19-9 and CEA; in addition, the modern imaging methods CT or MRT, including MRCP and MR-angiography, were performed bi-monthly. The median survival of the 69 patients (65% metastasized stages) was 16 months. The median survival increased with the number of effective treatment sequences, for the whole group from 5 to 10 and 23 months in relation to 0, 1 and >1 effective sequences respectively. The results support our concept of EOSPC in pancreatic cancer patients, compared to clinical studies following protocols with only 1 treatment sequence and median survival rates of no more than 6-9 months. Compared to the efficacy-orientated sequential polychemotherapy (EOSPC) concept, which does not exclude but also allows the inclusion of clinical trials for further evaluation of new drugs or drug combinations, the common practice looking for survival in studies following protocols with only 1 treatment sequence might represent a negative predictive factor with respect to overall survival, as can be demonstrated by a comparison of our data with relevant recent literature. Our results further indicate that the interest of the clinicians and companies should not be focused only on first-line therapies, but also on 2nd- and 3rd-line strategies, as in our patients a second- and third-line therapy could be started in 73% and 68% of the patients respectively.*

The majority of studies published during recent years still report on the results of a single treatment regimen in relation to survival of pancreatic cancer patients. In these presentations, no details are reported on second- or third-line therapies at all, or whether second-/third line therapies were given in an individual or prospectively planned sequence. The median survival in these studies following protocols with only 1 treatment sequence again amounted to no more than 6-9 months (1-13), in contrast to our data on efficacy-orientated sequential polychemotherapy (EOSPC) with overall median survival rates of 12 and more months, based on our clinical experience (14-16).

Therefore, the treatment and survival data of patients admitted to our unit in 2004, who were treated by us or in close cooperation with us, were analysed. The follow-up was mainly based on monthly determinations of the tumor markers CA 19-9 and CEA, complemented by bi-monthly performed CT / MR imaging methods in addition to the common laboratory and clinical investigations.

The aim of the study was not to evaluate the superiority of one single regimen, but to examine the possibility of improving survival of pancreatic cancer patients by a sequence of chemotherapeutic drugs or drug combinations.

Patients and Methods

Patients. Sixty-nine pancreatic cancer patients, 38 males, 31 females, aged 31-77 (median 60) and 39-73 (med 60) years, suffering from exocrine pancreatic cancer of the head (n=60), corpus (n=5) and cauda (n=4) respectively, admitted in 2004 with start of treatment before or within 2004 were studied.

The patients suffered from proven non-resectable pancreatic exocrine cancer (n=43) without (n=16) or with liver metastases (n=27), or tumor recurrence (n=26) without (n=8) or with distant metastasis (n=18). G1 /G2 and G3 tumors were found in 3%, 66% and 31% of patient respectively.

Treatment regimens. Gemcitabine was applied as monotherapy (1000 mg/m^2 weekly as commonly used) or in combinations. Gemcitabine + mitomycin-C (3-week regimen; day 1: 7 mg/m^2 mitomycin-C over 30 min followed by 450 mg/m^2 gemcitabine over 60 min; day 8 and 15: 450 mg/m^2 gemcitabine over a period of 90 min. Day 21 was the first day of the second cycle. In the locoregional approach, mitomycin-C + gemcitabine were given at day 1 *via* a catheter inserted in the celiac trunk or into the hepatic artery, gemcitabine at day 8 and 15 intravenously) (14, 17, 18).

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5-Fluorouracil/folinic (5FU/FA) acid was applied *via* the central venous system according to Ardalan *et al.* (19). Irinotecan was applied weekly either as monotherapy (85 mg/m^2 over 90 min) or in combination with 5FU/FA, based on previous studies (20).

Gemcitabine in combination with oxaliplatin was given as described elsewhere (21).

Oxaliplatin was given in combination with 5FU/FA. Day 1: oxaliplatin (80 mg/m^2 over 2 h) + 5FU/FA; day 8: 5FU/FA. Day 14 was the first day of the second cycle.

In single patients, other drug/drug combinations were tried: gemcitabine in combination with pemetrexed (international first-line study), capecitabine alone or in combination with gemcitabine or oxaliplatin, and taxotere as monotherapy.

Follow-up. Follow-up was mainly based on clinical signs as well as on tumor marker determinations (CA 19-9 and CEA) every 4 weeks and on the results of bi-monthly performed CT or/and MR including MRCP and MR angiography. Ultrasound (US) was used mainly to look for ascites and in the case of clinical signs needing acute differential diagnosis of diseases of the biliary tract system and the pancreas.

In 52 patients, CA 19-9 represented the most relevant tumor marker, in 5 patients CEA. Twelve patients did not show elevated levels of either tumor markers at time of commencing chemotherapy. In these patients, the follow-up was mainly based on the results of the imaging methods CT/MR using the conventionally accepted response criteria.

Based on our previously published results indicating a more rapid and sensitive response of CA 19-9 to tumor treatment compared to the imaging methods, the tumor response in this study was mainly based on the results of the tumor marker determinations except from the 12 patients not expressing tumor markers at the beginning of the treatment.

The imaging methods were mainly used for pretherapeutical staging, in order to avoid potential misinterpretations of tumor marker serum curves in the case of concomitant biliary infections, to diagnose local or distant complications, and for future analyses needing a comparison of our data with those of other groups mainly using imaging methods for follow-up.

Tumor response criteria. Tumor marker response was analysed in relation to the generally accepted morphological criteria: CR (complete response): decrease into the normal range, PR (partial response): decrease below 50% of the initial values, MR (minor response): decrease to values between 25-50% of the initial values SD (stable disease): +/– 25% of the initial values over a time period of more than 2 months, PD (progressive disease): increase to more than 25% of the initial values in 2 or more determinations.

A progress of the tumor disease was also diagnosed in the case of a significant increase of the tumor marker levels (>25%) even in the case of an only slight increase of the tumor lesions in the imaging methods (>10%).

Efficacy-orientated sequential polychemotherapy (EOSPC). First-line therapy mainly consisted of gemcitabine monotherapy (n=53), a combination of gemcitabine+mitomycin C (14), given intravenously (n=8) or locoregionally (n=6), as well as gemcitabine + pemetrexed (n=2).

Second-line treatment was performed in 50 patients with 24 h infusion with 5FU/FA (n=30), gemcitabine+mitomycin-C (n=12, intravenously n=6, intraarterially n=6) and gemcitabine +5FU/FA (n=1), gemcitabine mono (n=2), Fu/FA (n=1), capecitabine (n=1), 5FU+irinotecan (n=1) and taxotere (n=2), respectively.

Third-line therapy in 47 patients comprised 5FU/FA (n=14), 5FU/FA+irinotecan (n=6), 5FU/oxaliplatin (n=7), capecitabine+oxaliplatin (n=1), 5FU+oxaliplatin (n=7), irinotecan (n=3), gemcitabine mono (n=3) and gemcitabine+mitomycin-C (n=6; intravenously n=4, intraarterially n=2).

A fourth-line therapy was started in 15 patients with 5FU/FA alone (n=1) or in combinations with oxaliplatin (n=3), irinotecan (n=2) or gemcitabine (n=1), with irinotecan (n=2) or with gemcitabine (n=2), gemcitabine+mitomycin-C (n=3 intravenously) or in a single case with cetuximab+gemcitabine.

Tumor marker determinations. The tumor markers CA 19-9 and CEA were determined following international quality control recommendations (22, 23). Aliquots of serum samples were additionally stored at –70˚C in order to improve the results by redetermination if desired. CA 19-9 was determined using a Kryptor system (BRAHMS, Henningsdorf, Berlin, Germany), CEA using the ELECSYS system (Roche).

Supportive care. In addition to palliative chemotherapy in all patients, we also stressed the actual possibilities of supportive therapy, pain therapy, nutrition including supplements and parenteral home nutrition *via* port systems, as well as antiemetics, palliative surgical endoscopy (biliary stents/PTCD/ intestinal, and in one case also repeated colonic stents).

Results

Our results in patients admitted to our unit in 2004 comfirm our previous data in so far that the overall survival for pancreatic cancer patients increases with the number of effective treatments up to median survivals of 18.5 (M1 stages) and 27.5 months (M0 stages) for patients with >1 effective treatment on the basis of the tumor marker analyses, *i.e.* for 62% of the M0 tumors and 49 % of the M1 tumors (Figure 1).

The overall survival of all 69 patients treated within this period was 16 months. The overall survival for the M0 tumors (n=31) was 18 months and for the M1 tumors (n=38) 13 months.

These survival data are comparable to those reported during recent years (14-16).

In addition, we analysed our data for the relation between the number of effective treatments and the survival. Even these data support the concept that survival increases in relation to the number of effective treatments. In relation to 0 effective and 1 or >1 effective treatments, we found a median survival for all 69 patients of 5 (n=9), 10 (n=22) and 23 (n=38) months respectively (Figure 1).

The individual data are shown in Figure 2. The grey bars represent patients still alive at the time of evaluation.

The combination of gemcitabine + mitomycin again proved a rather effective treatment regimen. In the 15 first-line

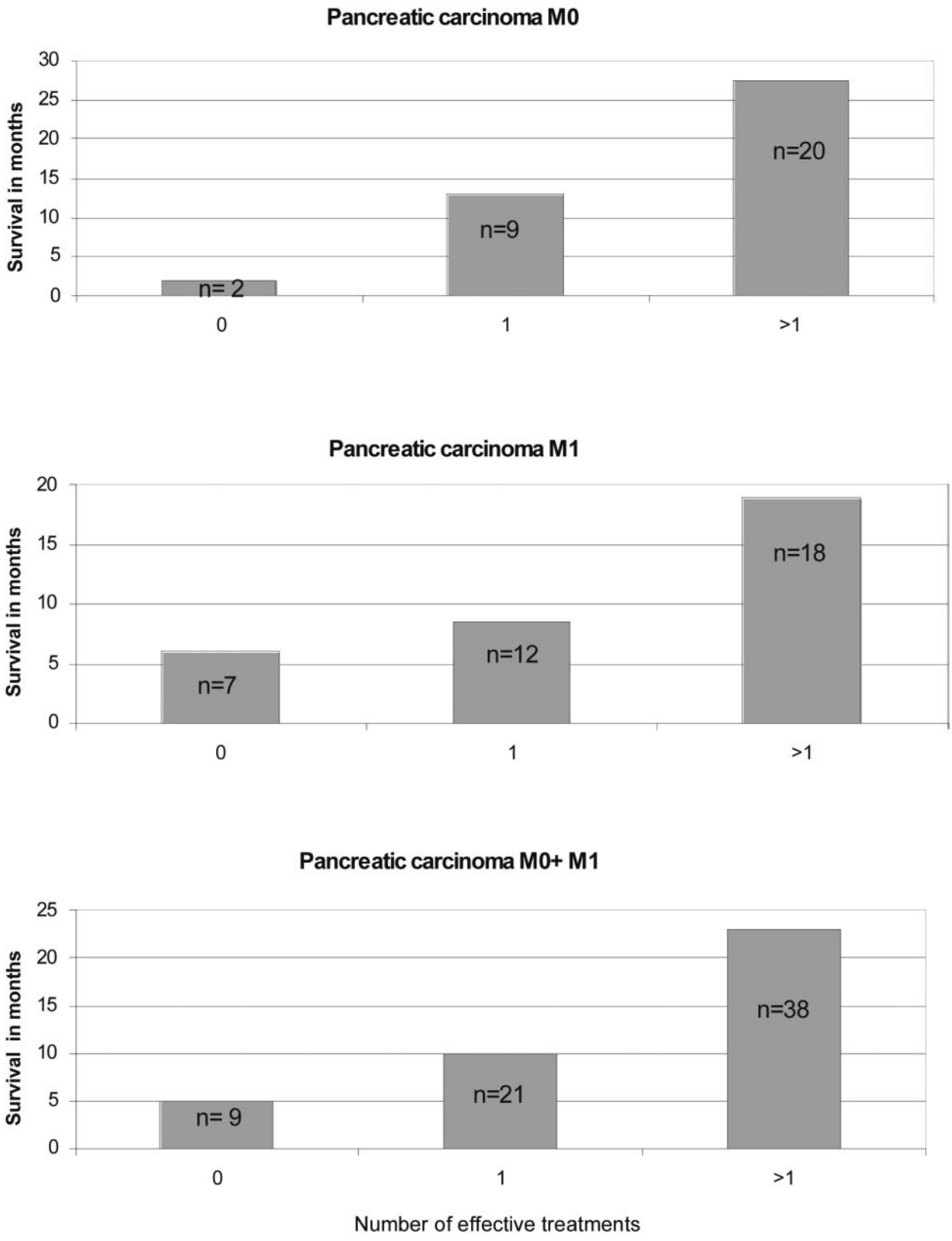

Figure 1. *Median survival (months) of pancreatic cancer patients in relation to the number of effective treatment sequences, demonstrated for advanced disease without distant metastasis (M0), metastasized stages (M1) and the whole group of patients (M0+M1).*

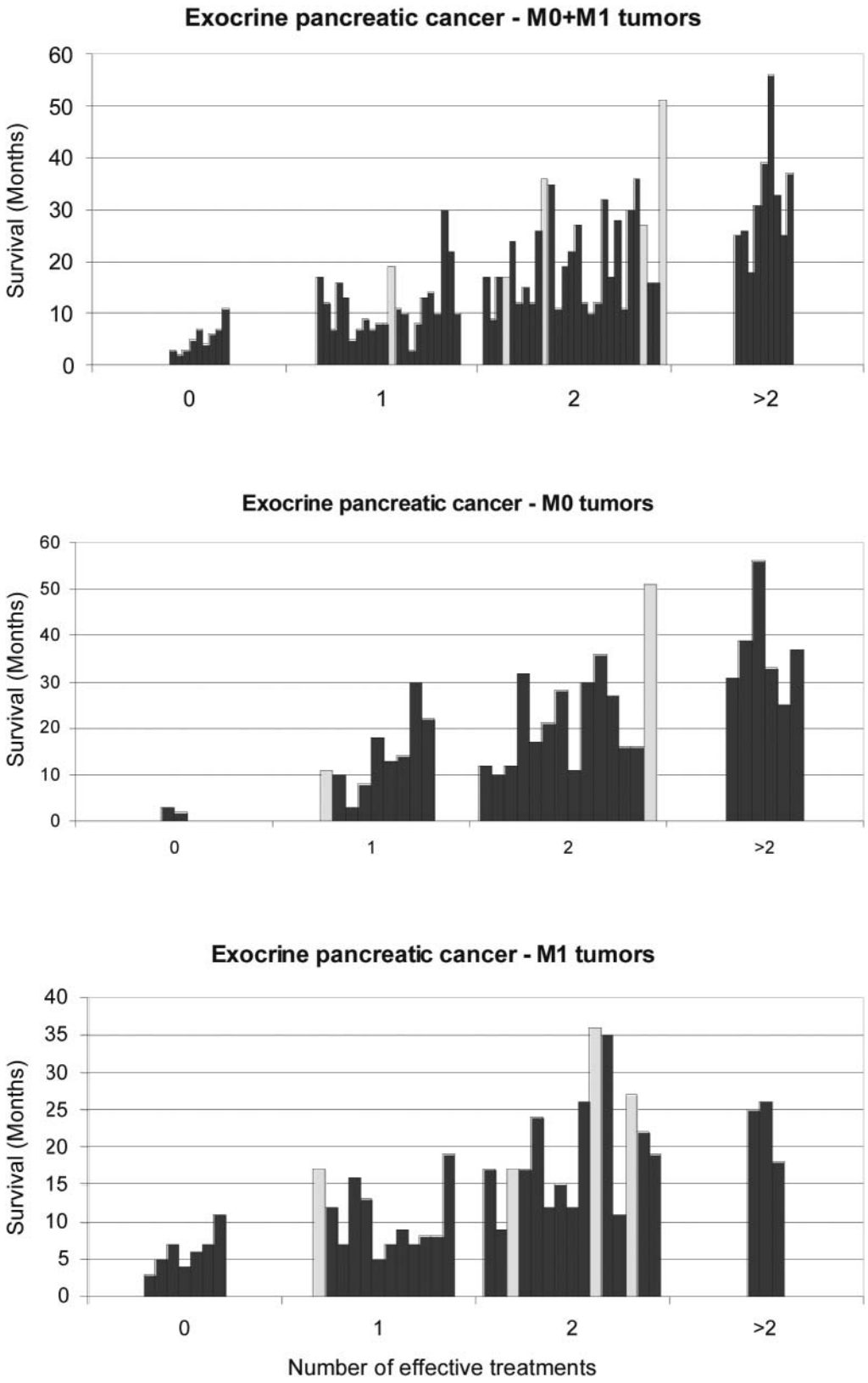

Figure 2. *Survival (months) of 69 patients admitted with pancreatic cancer in relation to the number of effective therapies, demonstrated for advanced disease without distant metastasis (M0), metastasized stages (M1) and the whole group of patients (M0+M1).*

treatments we diagnosed CR, PR, MR and SD in 1/14, 5/14, 5/14 and 3/14 patients respectively, based on CT/MR imaging methods and 3/14, 6/14, 1/1 and 2/14 patients based on the course of the relevant tumor markers. Second-line therapy with gemcitabine+mitomycin-C was performed in 12 patients with the following results: PR in 9 patients on the basis of the tumor marker determinations, as well as MR in 2 and 3, and SD in 1 and 7 patients on the basis of serum tumor markers curves and the imaging methods respectively.

Analysing the number of different treatment regimens tried in our 69 patients in 2004, we found that 50/69 patients (73%) presented the opportunity for a second-line treatment, 47/69 (68%) for a third-line treatment in the case of follow-up by serial tumor marker determinations (monthly), as well as bi-monthly cimaging methods.

Discussion

The presented data further support the concept that an efficacy-orientated sequential polychemotherapy seems to improve the survival of pancreatic cancer patients, in locally advanced, as well as metastasized stages, in relation to the number of effective treatment lines.

In contrast to our data, clinical studies looking for median survival following protocols with only one treatment sequence report survival data of no more than 6-8 to 9 months, *e.g.* for gemcitabine alone (1, 2), gemcitabine in combination with oxaliplatin (5, 11) or irinotecan (4, 10) or mitomycin-C (9) or other cytostatics (13), for capecitabine (3), or combinations of gemcitabine with newer drugs like erlotinib (8, 12), bevacizumab (7) or pemetrexed (6).

However, in 2005, two further studies supported our concept that further treatments after a first-line treatment can improve survival. Oettle *et al.* demonstrated that a second-line therapy with 5FU/FA+oxaliplatin after first-line treatment with gemcitabine improved overall median survival by 6 weeks compared to a best supportive care arm (24). Moreover, in a study of 30 patients, Cantore *et al.* found that a second-line treatment with a combination of irinotecan+oxaliplatin improved median overall survival of patients with metastasized stages from diagnosis up to 16 months – after a first-line treatment with gemcitabine (n=17), 5FU (n=7) and a first-line therapy with gemcitabine followed by a therapy with intraarterial application of FLEC (n=6) (25).

Clearly, our clinical practice with EOSPC is not able to determine the superiority of one or the other treatment regimen in comparison to the others. However, our concept with a first-line therapy with gemcitabine alone or in combination, followed by second-line regimens with 5FU/FA alone or in combination and a third-line treatment with further gemcitabine combinations or 5FU/FA or irinotecan combinations seems to offer a good chance for pancreatic cancer patients to live longer than supposed by all the prospective randomized studies on survival after a single treatment.

The concept of EOSPC for pancreatic cancer patients also seems to be supported by results of a sequential chemotherapy study in patients suffering from colorectal cancer, published in 2004. Tournigand and coworkers demonstrated that a sequential therapy with FOLFIRI (first-line) followed by FOLFOX 6 (second-line), or FOLFOX 6 (first-line) followed by FOLFIRI (second-line) improves survival of colorectal cancer patients compared to survival after first-line therapy with FOLFOX 6 and FOLFIRI respectively, without second-line or further regimes (26).

Three further conclusions might be drawn from the data of our publications in 2000, 2003 and 2005 and the presented data here, supported by the publications of Oettle *et al.* (24) and Cantore *et al.* (25): 1) Individualized sequential treatment strategies seem to improve survival of pancreatic cancer patients compared to that suggested by clinical studies on survival after treatment with only one sequence. This sequential concept does not exclude the performance of clinical studies. Clinical studies are essential for evaluation of the efficacy of new drugs and/or drug combinations. However, in order to evaluate a new drug or new drug combination, clinical studies should include a sequential strategy with at least 2 or 3 treatment sequences described within the protocol in detail. 2) Companies and institutions should not only look for the activity of new drugs or drug combinations in first-line treatment studies, but also for their potential activity as second- or third-line therapies, as modern follow-up in our studies allowed a second-line therapy in 73% of our patients admitted in 2004, and a third-line therapy in 68%. 3) Prospective randomized studies as mainly published during recent years, only looking for the effects of first-line therapies on survival and therefore neclecting the possibility of second- or third-line therapies, might have a negative influence on survival of pancreatic cancer patients.

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