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LETTER TO THE EDITOR

Timing of start of systemic treatment in patients with asymptomatic metastasized pancreatic cancer (TIMEPAN): a protocol of a multicenter prospective patient preference non-randomized trial

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Introduction

Pancreatic ductal adenocarcinoma is one of the deadliest forms of cancer with a 5-year survival of less than 5% for patients with metastatic disease (mPDAC) [1]. Due to increased use of imaging, the number of asymptomatic patients diagnosed with mPDAC cancer is increasing [2–4]. In some cases the primary diagnosis of asymptomatic mPDAC is detected on a scan performed for an unrelated indication, but in many cases standard follow-up scans after the inclusion of patients in neo-adjuvant and adjuvant trials leads to the early diagnosis of metastases. To illustrate this, in the Netherlands 97% of patients after pancreatic surgery undergo imaging during follow-up to detect potential recurrence, subsequently 24% off the patients diagnosed with local or distant recurrence is asymptomatic at diagnosis [5].

For these patients, palliative systemic treatment is the only tumor-targeted treatment option. Use of gemcitabine plus nab-paclitaxel (GEM-NAB) or the FOLFIRINOX regimen (5-fluorouracil, oxaliplatin, irinotecan and leucovorin) increased survival up to 9–11 months, compared to 7 months for gemcitabine monotherapy [6,7]. Furthermore, in patients with symptomatic mPDAC, palliative chemotherapy can decrease tumor burden, and thereby diminish disease symptoms and improve quality of life (QOL) [8]. Nevertheless, chemotherapeutic agents also have negative side effects. Use of modern multi-agents chemotherapies are associated with serious adverse events (i.e. grade 3–4), with an incidence up to 46% during FOLFIRINOX [6]. Therefore, in patients with asymptomatic mPDAC, the potential benefits of palliative chemotherapy must be carefully weighed against the potential negative side effects.

To date it is unclear whether early start of treatment in asymptomatic cancer patients is associated with improved survival rates. A recent systematic review including asymptomatic cancer patients emphasized that only limited evidence is available on timing of treatment initiation in asymptomatic patients, only five studies have been performed on this topic [9]. Within this limited available evidence, delayed start of chemotherapy did not worsen survival, while it could preserve QOL. For patients with asymptomatic mPDAC specifically, no literature is available on this topic. The aim of this study is to investigate the effect of immediate versus delayed treatment on quality adjusted overall survival in patients with asymptomatic mPDAC.

Methods

Study design, setting, and aim

The TIMEPAN trial is a multicenter prospective patient preference non-randomized trial. The trial was originally initiated as a randomized controlled trial, however due to strong patient preference for one of both treatment arms, only two patients were included in the first 20 months. To minimize selection bias and improve feasibility, the trial

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design was altered into a multicenter prospective patient preference trial. Patients with asymptomatic mPDAC can decide, upon patient preference, for arm A: immediate systemic treatment, or arm B: delayed systemic treatment. The study was designed in accordance with the STROBE guidelines [10].

Study population

All consecutive patients in participating centers will be evaluated for participation. Adult patients with asymptomatic mPDAC and no prior chemotherapy for metastatic disease are eligible. The absence of disease-related symptoms is specified as (at inclusion): no pain requiring regular narcotic analgesics, no weight loss over 5 kg within the past three months (unless related to surgery or other illness), no persistent nausea requiring medication, no obstructive bowel symptoms, no persistent fever related to metastatic cancer, and no other symptom which in the opinion of the clinician was due to metastatic cancer.

Additional inclusion criteria are: histologically or cytologically confirmed cancer of the pancreas; measurable metastatic disease on computed tomography (CT) scan per RECIST version 1.1 [11]; Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–1; life expectancy $\geq$ 3 months; a negative urine or serum pregnancy test within 7 days before first dose of study medication if female subject is of childbearing potential; no abnormalities in clinical laboratory values (absolute neutrophil count, aspartate aminotransferase, alanine aminotransferase, serum creatinine or creatinine clearance, prothrombin time, partial thromboplastin time, and platelet count).

Exclusion criteria are: known central nervous system involvement or brain metastases; New York heart association class III or IV cardiac disease or myocardial infarction within the past 12 months; inability to comply with the study and follow-up procedures as judged by the Investigator; and women currently breastfeeding. In addition, patients with any other finding that leads to reasonable suspicion of a disease or condition that either 1) contraindicates the use of systematic treatment, or 2) may affect the interpretation of the results, or 3) render the subject at high risk for treatment complication, are excluded.

Treatment

After written informed consent is signed, all patients will undergo eligibility assessment within 14 days prior to starting the study. After confirmation of eligibility, patients can choose the preferred arm. Immediate systematic treatment (arm A) is defined as: initiation of systemic therapy within three weeks of date of diagnosis. Patients will receive either (m)FOLFIRINOX or GEM-Nab, determined by shared decision making of the medical oncologist and patient. Every two weeks a cycle of (m)FOLFRINOX will be scheduled (day 1), every four weeks for GEM-NAB (day 1, 8 and 15). Delayed systematic treatment (arm B) is defined as: delayed initiation of systematic therapy until development of disease-related symptoms. Every four weeks, development of symptoms will be assessed. Patients that develop symptoms during follow-up, will start chemotherapy conform the direct treatment arm.

Follow-up and data collection

Regardless of the treatment arm, follow-up appointments and QOL measurements are scheduled every four weeks, and tumor evaluation every eight weeks (Figure 1). Clinical data will be collected using a secured electronic database (CASTOR EDC, CIWIT B.V., Amsterdam, The Netherlands). During follow-up visits, the following items are recorded in the electronic case record files (ECRF) by the treating physicians: current medication, WHO performance status, vital signs, weight, laboratory results, and adverse events. Additionally, each month patient reported outcomes will be evaluated using the infrastructure of the *Dutch Pancreatic Cancer Project (PACAP)* [12]. Patient reported outcomes include: EORTC Quality of Life Questionnaire (QLQ) Cancer Module (C30), EORTC QLQ Pancreatic Cancer Module (PAN26), and the EQ-5D-5L [13–15]. The tumor response evaluation include a CT scan (response according to RECIST is evaluated), and level of CA 19.9. Data will be handled confidentially, and an individual subject identification code is used to link the data to the subject. The study coordinators safeguard the key to the code and access to the coded data will be restricted to the principal investigators, the coordinating investigator, the study coordinators and the monitor.

Safety

Adverse events will be assed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [16]. All adverse events classified as grade 3–5 will be recorded on the case report forms. Serious adverse events (SAEs) will be collected and recorded throughout the study period, starting at day 1 of the treatment though to 30 days

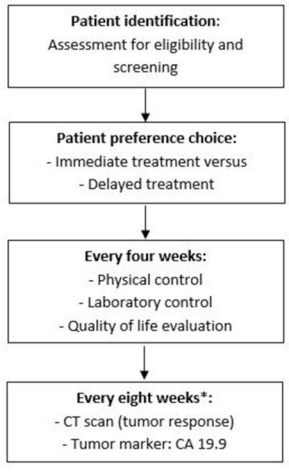

Figure 1. Follow-up TIMEPAN study. *These are the additional assessments every eight weeks, also physical, laboratory control and quality of life evaluation will take place.

after the last dose of the investigational product (systemic treatment). The (local) investigator should notify the primary investigator (or its delegate) within 24 h of learning of its occurrence in accordance with local procedures, statues, and the European Clinical Trial Directive. The study will be monitored by the Clinical Monitoring Center (CMC) of the Amsterdam UMC. Thereby, the primary investigator (or its delegate) will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board, and competent authorities of the concerned Member. Moreover, an independent data safety and monitoring committee (DSMB) has been assigned to evaluate safety parameters at regular intervals. An interim analysis will be carried out after 33% of the intended data collection has been achieved under the supervision of the DSMB and will address the question whether sufficient conditional power remains to reject the null hypothesis of non-inferiority (futility analysis).

Primary and secondary outcomes

Primary outcome is quality adjusted overall survival. This is defined by the quality of life score (so called 'utility score', evaluated using the EQ-5D questionnaire) combined with the overall survival in months (starting from date of diagnosis of mPDAC i.e. date of imaging or pathology). The primary endpoint will be evaluated by comparing the area-under-the-curve of both groups. Figure 2 depicts an example of the analysis. To illustrate, patient 1 (orange line) chooses for delayed treatment, after diagnosis (month 0) his quality of life scores gradually creased from 70 to 50 over eight months, at nine months he is deceased. The patient in blue choses for direct treatment, after he starts treatment at diagnosis his quality of life decreased from 70 to 50 in one month, after which it slowly decreases to 41 over ten months, at eleven months he is deceased. The area under the curve for the orange patient (515) is compared to the area under the curve of the blue patient (490). The example includes only one patient in both groups, the formal analysis will include the mean area under the curve of all patients in both groups.

Secondary outcomes include time to disease progression, quality adjusted progression free survival, overall survival, duration of time without symptoms of disease progression or toxicities, adverse events, change in CA 19.9, and strength of preference for the chosen treatment arm.

Sample size calculation

A sample size is calculated for 184 patients (92 in each group), taking into account 10% loss to follow-up (added to 166 patients, 83 per arm). Accrual will be continued in both arms until 92 patients within each arm are included. When the sample size in each group is 83, a two group 0.025 one-sided t-test will have 80% power to reject the null hypothesis that delayed treatment is non-inferior to immediate treatment (the difference in mean quality adjusted overall survival scores, Mdelayed - Mimmediate, is minus 20 or farther from zero in the same direction) in favor of the alternative hypothesis that the delayed treatment is non-inferior, assuming that the expected difference in means is 15 (=675–660) and the common standard deviation is 80 (based on ranges of 400 and $n = 92$ per group).

Study duration

Trial opened for accrual 22th April 2021, and the adjustment of study design (i.e. prospective patient preference instead of randomization) was approved by the Medical Ethical Board on the 18th of January 2023. As five patients per months are expected to be recruited for this study, patient accrual is expected to be completed in 36 months after approval of the new study design. An additional one-year follow-up is expected to be required until endpoints are met.

Statistical analysis

Descriptive statistics will be used to assess baseline characteristics. Results will be reported as proportions for

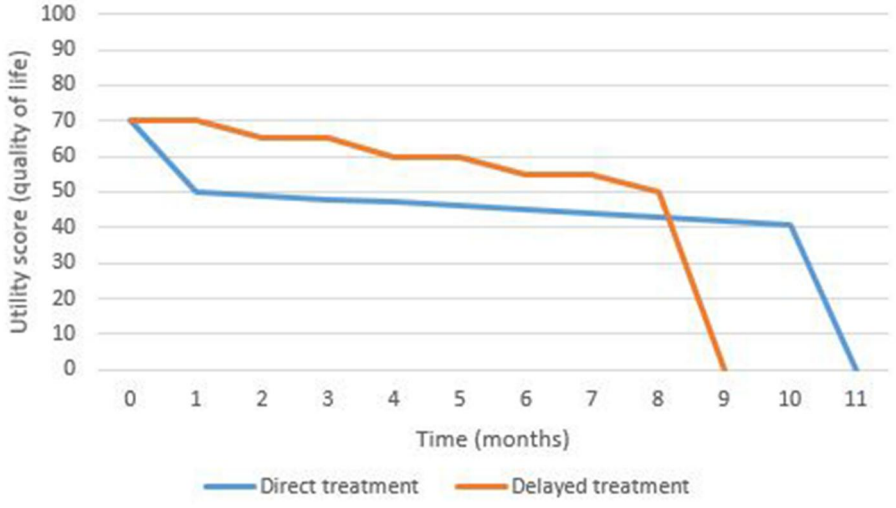

Figure 2. Example of quality adjusted survival curve.

categorical variables, and as mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables. Normally distributed data will be compared using a Students-t-test, categorical data using the chi-square test, and non-normally distributed data using the Mann Whitney U test. Baseline values will be imputed by multiple imputation, outcome variables will not be imputed.

Primary analysis includes linear regression analysis comparing quality adjusted overall survival among the two groups. Quality adjusted overall survival will be calculation by using the individual monthly utility scores of the EQ5D questionnaire, and the survival in months, for the total study period [17]. For each patient the area under their quality of life adjusted overall survival curve (X-axis time, Y-axis utility) will be provided, reflecting their quality adjusted overall survival score [18]. A linear regression will be performed on quality adjusted overall survival score. Within this linear regression, IPTW weighting will be used to balance baseline characteristics that attribute to the choice of treatment arm [19]. The propensity of being exposed to one of the treatment groups will be calculated based on clinically relevant baseline characteristics (i.e. age, sex, performance status, comorbidities, hospital, recurrence/primary disease, amount of metastases, and number of organs with metastases) and the strength of the preference for the chosen treatment arm measured by a five-point Likert scale included in the ECRF. Weights will be calculated as the inverse of propensity score. The linear regression will include the inverse probability weight (eliminating confounders on treatment choice). The lower limit of the confidence interval of the beta for the delayed group compared to the control group will be compared to the non-inferiority margin. Subgroup analyses will be performed to explore whether specific groups of patients seem to benefit most from treatment arm A or B. Secondary survival outcomes will be evaluated using linear regression models, Kaplan Meier curves, or Cox proportional hazard models, as appropriate.

All P values will be based on a 2-sided test. A P value of below 0.05 is considered to be statistically significant.

Discussion

Evidence on the optimal timing of treatment initiation in patients with asymptomatic mPDAC is currently lacking. Traditionally, systemic therapy is initiated immediately following disease detection with the assumption that this benefits survival, even though delaying systemic therapy might preserve QOL and avoid therapy-related toxicity in asymptomatic patients. This is the first study investigating the optimal timing of systemic treatment initiation in patients with asymptomatic mPDAC.

Delayed initiation of systematic therapy in patients with asymptomatic cancer has only been studied in metastatic colorectal, ovarian, and gastric cancer patients [9]. Within this limited available evidence, delayed start of chemotherapy did not worsen survival, while it could preserve QOL. Compared to these types of cancer, mPDAC has far worse prognosis with a 5-year survival of 3%, compared to 6% in metastatic gastric cancer, 14% in metastatic colorectal cancer, and 30% in metastatic ovarian cancer [20]. This questions whether these results can be generalized to patients with mPDAC. It can be hypothesized that patients with mPDAC, especially given their very poor survival rates, would prefer maintaining a relatively good QOL without hospital visits, instead of deterioration of QOL due to early start of systematic treatment. This can be supported by a recent survey among 459 advanced cancer patients, of which 55% equally valued QOL and length of life, whereas 27% preferred QOL and only 18% length of life [21]. On the contrary, the poor survival of mPDAC is associated with aggressive biological behavior [1]. Therefore, it could be hypothesized that treatment should be started early, in order to not lose the window of opportunity for systemic treatment, as rapid progressive disease could enable patients to start systematic treatment at all due to a worsened physical status. Nevertheless, only retrospective studies have been performed investigating the effect of time on prognosis, showing contradictive results [22,23].

A survey including all first and last authors of published clinical trials in mPDAC, concluded that the majority of medical oncologist (63%) preferred starting treatment directly after diagnosis in patients with mPDAC [24]. However, in one-third of cases delayed treatment was favored (case context: just one small lung metastasis, older age, significant comorbidities). Additionally, within this survey the choice on timing of treatment initiation differed among countries, and years of experience as a medical oncologist. This heterogeneity emphasizes the lack of evidence and equipoise on this topic, and the need for further investigation.

The primary outcome of this study consists of the composite outcome quality adjusted overall survival. This provides a unique opportunity to take into account the actual consequences for the patient in clinical practice [18]. Often in cancer trials, endpoints such as tumor response, survival, and toxicity are used. While these endpoints are valid for an explanatory interpretation of the treatment (describing biological differences), they can be considered inadequate for a pragmatic interpretation of trial results, deciding on which treatment is likely to benefit an individual patient. In the TIMEPAN trial, one of the treatment arms can show an advantage on some endpoints, but a disadvantage on the other (for example better response, but more toxicity). Therefore, quality adjusted overall survival is expected to be the most clinically relevant outcome. Clinicians and policymakers recognize the importance of measuring QOL if evaluated with valid (really measure what they are supposed to measure), reliable, and responsive (able to take important changes in QOL of a period of time – even if they are small) instruments [25]. Consequently, the validated EORTC cancer specific QOL questionnaire (EORTC-QLQ-C30), pancreatic cancer specific questionnaire (EORTC-QLQ-PAN26) and EQ-5D-5L are used [13–15]. A concern within this trial, however, might be the lower response rate of patients in the final stages of life. A recent Dutch retrospective study including the PACAP PROMs (same infrastructure as within this study), showed that of the 138 included patients that received palliative

systematic treatment and answered a QOL questionnaire, only 59% completed the 3-months follow-up questionnaire, and this was 29% at 9-months [26]. Nevertheless, this will be expected to be the same for patients in both treatment arms.

Performing RCTs is considered to be notoriously difficult. To illustrate, one in five surgical RCTs is being discontinued early and one in three completed trials remain unpublished [27]. Problems in RCTs are mainly poor recruitment, patient drop-out due to disappointment bias in the control arm, and high costs [28–30]. Recruitment problems were evident within the TIMEPAN trial. Therefore, this trial can be an example of how an RCT can be adjusted, in this case by changing the design into a prospective non-randomized study, to still answer the research question. A concern of this adjustment is the introduction of selection bias, as it is possible that a selected group of patients will choose a particular treatment arm. To increase the generalizability of our results, within our analysis IPTW weighting will be used [31]. Within this type of analysis, baseline characteristics that contribute to the choice of the treatment arm will be balanced by adding an inverse probability weight (calculated based on clinically relevant baseline characteristics that contribute to the choice of treatment arm). Unfortunately, by using IPTW weighting one cannot correct for unknown baseline characteristics that might attribute to the choice, such as the psychological beliefs of the effect of chemotherapy upon the timing of treatment initiation Moreover, patients could underscore adverse events/symptoms as they have chosen for the treatment arm themselves. This will be partly overcome, as the treating physician score the adverse events. Nevertheless, patient reported outcomes can be affected. Nevertheless, keeping the randomization within the trial, would also introduce selection bias, as only patients that do not have a strong preference (the minority) will be included within this trial. Thereby, patients randomly allocated to their non-preferred intervention may experience resentful demoralization, resulting in poor adherence to treatment or reporting of worse outcomes [32]. Especially subjective (patient reported) outcomes, the primary outcome of this study, are prone for this bias [33]. Changing the study design to a patient preference prospective cohort seems the only feasible option to answer the research question as well as possible.

In conclusion, systemic therapy is traditionally initiated immediately following disease detection. Nevertheless, delaying chemotherapy might preserve QOL and avoid therapy-related toxicity in asymptomatic patients, whereas the impact on survival is unknown. This is the first trial comparing the effect of immediate systematic therapy to delayed systematic therapy on quality-adjusted overall survival in patients with asymptomatic mPDAC.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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