A randomised controlled trial of gemcitabine hydrochloride plus S-1 combination therapy versus gemcitabine hydrochloride therapy alone in pancreatic cancer patients aged ≥75 years: a study protocol for an open-label randomised feasibility study

Hiroshi Ishii, Natsumi Yamashita, Makoto Ueno, Shinichi Ohkawa, Akiko M Saito, Mitsugu Sekimoto

ABSTRACT

Introduction In Japan, the age of patients with pancreatic cancer has increased. Combination chemotherapies such as 5-fluorouracil/leucovorin, oxaliplatin and irinotecan therapy and gemcitabine hydrochloride (GEM) + nab-paclitaxel therapy have been developed as the standard treatments for young patients with advanced recurrent pancreatic cancer. However, both therapies produce toxicity and their administration is limited by the patients' age or performance status. The efficacy and safety data obtained in the GEST study—a large-scale randomised controlled study conducted in patients with pancreatic cancer in Japan—suggested that GEM + S-1 (GS) combination therapy is a promising candidate for those aged between 75 and 80 years. However, for patients aged ≥80 years, no efficacy or safety data on GS therapy are currently available.

Methods and analysis This open-label, randomised phase II study will involve patients with advanced recurrent pancreatic cancer, aged ≥75 years, with favourable general conditions. Using the electronic data capture system, participants will be randomly allocated to groups with standard treatment (GEM therapy alone) and study treatment (GS therapy). The treatments will be administered until the conditions meet the discontinuation criteria. The primary endpoint is overall survival.

Ethics and dissemination This trial has been approved by the National Hospital Organisation’s Central Review Board (H28-NHOD-01).

Discussion This study will reveal if GS therapy could be a standard treatment option for elderly patients with pancreatic cancer, by clarifying its efficacy and safety.

Trial registration number UMIN000025747; Pre-results.

INTRODUCTION

Invasive pancreatic ductal carcinoma accounts for about 90% of all pancreatic cancers, and is an intractable cancer with a 5-year survival rate of 2%–3%. In 2013, the number of pancreatic cancer-related deaths was 30,672, in Japan; in recent times, this figure has increased by 2.5 times. The numbers of incidences of and deaths from pancreatic cancer are almost identical. This disease accounts for 6% of all cancer-related deaths in Japan and is the fourth leading cause of such deaths, following cancers of the lung, stomach and large intestine.

Japan’s population is rapidly ageing, and the average age of patients with pancreatic cancer in the country has increased. In 2011, of the 33,095 patients with pancreatic cancer, the proportion of those aged ≥75 years was approximately 50% (75–79 years old; 5818, 80–84 years old: 5026 and ≥85 years old: 5691).

Resectable cases—diagnosed as Union for International Cancer Control (UICC) stage I/II—account for about 15% of all pancreatic cancer cases, the median survival time (MST) after standard treatment (surgical resection + postoperative adjuvant chemotherapy) is about 20 months, and the 5-year survival rate is about 20%. Unresectable stage III cancers (locally advanced cases)—due to the invasion of the surroundings by the primary pancreatic lesion, despite distant metastases not being clearly observed—account for 35% of all cases, and the MST after standard treatment (gemcitabine hydrochloride (GEM) therapy alone)² is 8–15 months. Stage IV cases with distant metastases (distant metastasis...
cases) account for about half of all cases, and the MST of patients who receive standard treatment including oxaliplatin/irinotecan hydrochloride hydrate/fluorouracil/levofolinate calcium combination therapy (FOLFIRINOX) therapy, developed potent combination chemotherapies such as FOLFIRINOX therapy and GEM + nab-PTX therapy are the standard treatments for young patients with favourable general conditions (performance status (PS) 0–1). However, FOLFIRINOX therapy is not an appropriate indication for elderly patients with pancreatic cancer because of its strong toxicity, which is associated with conditions such as neutropaenia, nausea, diarrhoea and fatigue. GEM + nab-PTX therapy is also relatively toxic, and its indication for patients with pancreatic cancer with poor general conditions (PS 2) is markedly limited.

S-1 is a new oral fluoropyrimidine derivative in which tegafur is combined with two 5-chloro-2,4-dihydroxypyridine modulators and oteracil potassium, a potentiator of fluorouracil’s (5-FU’s) antitumour activity that also decreases gastrointestinal toxicity.

A phase III trial (GEST study) compared therapy with S-1, with GEM alone, and with GEM plus S-1 (GS) in patients with advanced pancreatic cancer, in Japan and Taiwan, and the efficacy and toxicity of S-1 therapy were found to be similar to those observed in the case of GEM therapy, when it was used as a first-line treatment; thus, S-1 was judged to be non-inferior to GEM therapy.6

GEM therapy alone is the standard treatment for patients with advanced recurrent pancreatic cancer with poor general conditions (PS 2). It also may be the standard treatment for elderly fragile patients with pancreatic cancer although some physicians apply GEM + nab-PTX therapy for elderly patients with pancreatic cancer with excellent general conditions. However, efficacy and safety data on patients with pancreatic cancer aged between 75 and 80 years, as observed in a subgroup analysis of the GEST study,6 suggested that GS therapy is a promising candidate for elderly patients with pancreatic cancer.

Therefore, it is important to perform a randomised controlled study with the standard treatment—GEM therapy alone—and GS therapy; however, no efficacy or safety data are available for GS therapy in patients with pancreatic cancer aged ≥ 80 years. Therefore, it is necessary to perform a pilot study to decide whether this study could make progress to a confirmatory study in the following phase.

**Methods and Analysis**

**Study objectives**

This is an exploratory study to investigate whether GS therapy is feasible as a study treatment for the following phase III study, and the number of cases was set at 100 (standard treatment group: 50, study treatment group: 50), as the maximum number collectable within a 2-year period.

**Eligibility criteria**

**Inclusion criteria**

1. Having class IV or V adenocarcinoma, which, based on histological or cytological diagnoses consistent with imaging findings, is categorised as papillary adenocarcinoma, tubular adenocarcinoma, poorly differentiated adenocarcinoma or adenosquamous carcinoma.
2. Being diagnosed clinically and through imaging as locally advanced (UICC T4N0-1M0: stage III), distant metastasis (UICC M1: stage IV) and recurrence after the resection of pancreatic cancer.
3. No retention of coelomic fluid (pleural fluid and ascites) drainable by puncture, as observed on chest radiography and abdominal CT.
4. Age: ≥ 75 years at the time of registration.
5. PS (Eastern Cooperative Oncology Group) of 0 or 1.
7. Completion of at least 6 months after chemotherapy and radiotherapy for other cancers.
8. Satisfying all the conditions mentioned below. For all the test items, the latest test value within 7 days before registration will be adopted. The test performed on the same day of the week, 1 week before the registration day, will be accepted.
   i. White cell count: ≥ 3000/mm³ and ≤ 12 000/mm³
   ii. Haemoglobin level: ≥ 9.0 g/dL (without blood transfusion within 14 days before registration)
   iii. Platelet count: ≥ 10 × 10⁴/mm³
   iv. Albumin level: ≥ 3.0 g/dL
   v. Total bilirubin level: without biliary drainage, ≤ 2.0 mg/dL; with biliary drainage, ≤ 3.0 mg/dL.
   vi. Aspartate transaminase (AST) level: without biliary drainage, ≤ 100 IU/L; with biliary drainage, ≤ 150 IU/L.
   vii. Alanine aminotransferase (ALT) level: without biliary drainage, ≤ 100 IU/L; with biliary drainage, ≤ 150 IU/L. Biliary drainage will be applied employing a percutaneous (percutaneous transhepatic biliary drainage, or stent use) or endoscopic

**Study design**

This is an open-label randomised phase II study, the design of which is shown in figure 1. A single-arm phase II design could have been selected, but a randomised study setting with a standard treatment group was selected because there is no reliable historical data on the use of GEM therapy alone, for very old patients aged ≥ 80 years, with favourable general conditions.

**Study population**

This is an exploratory study to investigate whether GS therapy is feasible as a study treatment for the following phase III study, and the number of cases was set at 100 (standard treatment group: 50, study treatment group: 50), as the maximum number collectable within a 2-year period.

**Eligibility criteria**

**Inclusion criteria**

1. Having class IV or V adenocarcinoma, which, based on histological or cytological diagnoses consistent with imaging findings, is categorised as papillary adenocarcinoma, tubular adenocarcinoma, poorly differentiated adenocarcinoma or adenosquamous carcinoma.
2. Being diagnosed clinically and through imaging as locally advanced (UICC T4N0-1M0: stage III), distant metastasis (UICC M1: stage IV) and recurrence after the resection of pancreatic cancer.
3. No retention of coelomic fluid (pleural fluid and ascites) drainable by puncture, as observed on chest radiography and abdominal CT.
4. Age: ≥ 75 years at the time of registration.
5. PS (Eastern Cooperative Oncology Group) of 0 or 1.
7. Completion of at least 6 months after chemotherapy and radiotherapy for other cancers.
8. Satisfying all the conditions mentioned below. For all the test items, the latest test value within 7 days before registration will be adopted. The test performed on the same day of the week, 1 week before the registration day, will be accepted.
   i. White cell count: ≥ 3000/mm³ and ≤ 12 000/mm³
   ii. Haemoglobin level: ≥ 9.0 g/dL (without blood transfusion within 14 days before registration)
   iii. Platelet count: ≥ 10 × 10⁴/mm³
   iv. Albumin level: ≥ 3.0 g/dL
   v. Total bilirubin level: without biliary drainage, ≤ 2.0 mg/dL; with biliary drainage, ≤ 3.0 mg/dL.
   vi. Aspartate transaminase (AST) level: without biliary drainage, ≤ 100 IU/L; with biliary drainage, ≤ 150 IU/L.
   vii. Alanine aminotransferase (ALT) level: without biliary drainage, ≤ 100 IU/L; with biliary drainage, ≤ 150 IU/L. Biliary drainage will be applied employing a percutaneous (percutaneous transhepatic biliary drainage, or stent use) or endoscopic
**Exclusion criteria**

1. Determination of GEM +nabPTX therapy as introducible by the attending physician, with a request for the therapy by the patient.
2. The presence of an active advanced double cancer, with an expected life expectancy of <6 months.
3. The presence of bacterial infection requiring systemic antibiotic treatment by intravenous administration.
4. The presence of complications associated with mental illness or psychiatric symptoms (including dementia), and the study being judged as difficult for such patients to participate in.
5. Receiving continuous systemic (oral or intravenous) steroid administration.
6. The presence of pulmonary fibrosis or interstitial pneumonia (confirmed by chest radiography within 28 days before registration).
7. The presence of serious complications (heart failure, renal insufficiency, liver failure, haemorrhagic peptic ulcer, paralysis of the intestine, ileus and poorly controlled diabetes).
8. Complications associated with unstable angina (development or aggravation of an attack within the last 3 weeks) or myocardial infarction within 6 months.
10. Inability to use either iodine or a gadolinium contrast medium due to a drug allergy.
11. Being judged as ineligible to participate in the study by the principal investigator or subinvestigator.

**Study outline**

**Intervention**

The standard treatment group (group A) will receive outpatient treatment as a rule, but inpatient treatment at the time of introduction and other occasions will be appropriately accepted. The study treatment group (group B) will essentially receive inpatient treatment on days 1–8 of the first cycle because the safety of GS therapy for elderly adults has not been confirmed, and
it is important to take time for medication counselling, especially in the case of oral anticancer drugs for elderly patients. For GEM and S-1 therapies, the use of generic drugs will be accepted.

The dose will not be corrected with changes in the body weight after the initiation of treatment, because the median duration of treatment is expected to be less than a few months.

**Standard treatment group (group A): GEM therapy alone**

The drug will be administered through 30 min intravenous drip infusion employing the standard dosage and administration method: once a day at 1000 mg/m² on days 1, 8 and 15. A duration of 4 weeks (28 days) will be considered one cycle, and treatment will be continued until the condition meets the discontinuation criteria of the protocol treatment (refer to table 1).

When GEM cannot be administered on the specified day and time, due to patients’ convenience, the dosing day may be changed to 1 day before or after the schedule. When the dosing day is changed, no change corresponding to it will be made in the dosing schedule of the following cycle.

To prevent chemotherapy-induced nausea and vomiting, the administration of long-acting adrenocortical steroid as an antiemetic on the dosing day will be recommended. It will be administered on days 1 and 2 after the protocol treatment, depending on the patient’s condition. If the prevention efficacy is insufficient, 5-HT3 antagonist and NK1 antagonist will be administered. For patients with diabetes, the dose of the adrenocortical steroid will be appropriately reduced (dexamethasone sodium phosphate injection 6.6 mg → 3.3 mg → 1.65 mg).

**Study treatment group (group B): GS therapy**

GEM will be administered at a single dose of 1000 mg/m² on days 1 and 8 using 30 min intravenous drip infusion, and S-1 will be orally administered at a body surface area-based dose (60, 80 and 100 mg/day, table 2) divided into two, after breakfast and dinner, daily, for 14 days, followed by withdrawal for 7 days. Setting 3 weeks (21 days) as one cycle, treatment will be continued until the condition meets any of the discontinuation criteria of the protocol treatment (table 1).

When S-1 cannot be administered after breakfast on day 1, dosing may start after dinner, in which case administration will be continued until after breakfast on day 15.

When GEM cannot be administered on the specified day and time due to the convenience of the patient, the dosing day may be changed within 1 day before or after the schedule. When the dosing day is changed, no change corresponding to it will be made in the dosing schedule of the following cycle. When a patient stops taking S-1 by self-judgment or forgets to take it, its ingestion in the cycle will be skipped, and no drug will be administered to compensate for the shortage after day 15.

To prevent instances of chemotherapy-induced nausea and vomiting, the administration of long-acting adrenocortical steroid as an antiemetic on the dosing day will be recommended. It will be administered on days 1 and 2 after the protocol treatment, depending on the patient’s condition. If the prevention efficacy is insufficient, 5-HT3 antagonist and NK1 antagonist will be administered. For patients with diabetes, the dose of the adrenocortical steroid will be appropriately reduced (dexamethasone sodium phosphate injection 6.6 mg → 3.3 mg → 1.65 mg).

**Discontinuation criteria of the protocol treatment**

The protocol treatment will be discontinued under the following conditions:

1. Aggravation of the primary disease after treatment initiation, as judged by the principal investigator or subinvestigator. When the continuation of protocol treatment is clinically judged as appropriate even when the effect on the disease is judged as progressive on imaging, the protocol treatment will not be discontinued.

2. When protocol treatment cannot be continued due to adverse events.

---

**Table 1 Dose and dosing schedule**

<table>
<thead>
<tr>
<th>Group A</th>
<th>Dose</th>
<th>Day 1</th>
<th>Day 8</th>
<th>Day 15</th>
<th>Day 22</th>
<th>Day 29/day 1 of the following cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEM</td>
<td>1000 mg/m²</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>Withdrawal</td>
<td>○</td>
</tr>
</tbody>
</table>

**Table 2 Daily dose of S-1 and its division**

<table>
<thead>
<tr>
<th>Body surface area (m²)</th>
<th>S-1 dose (tegafur equivalent) (mg/day)</th>
<th>Division of daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.25</td>
<td>60</td>
<td>After breakfast 20 mg × 1 After dinner 20 mg × 2</td>
</tr>
<tr>
<td>≥1.25–&lt;1.50</td>
<td>80</td>
<td>20 mg × 2</td>
</tr>
<tr>
<td>≥1.50</td>
<td>100</td>
<td>25 mg × 2</td>
</tr>
</tbody>
</table>

GEM, gemcitabine hydrochloride.
i. When grade 4 non-haematotoxicity is observed, excluding the following adverse events: hypernatraemia, hypoponatraemia, hyperkalaemia, hypokalaemia, hyperglycaemia, hypoglycaemia, alkaline phosphatase, ALT, AST, total bilirubin, amylase, lipase and γ-glutamoyl transphosphatase. Non-haematotoxicity represents adverse events other than anaemia, a reduction in the number of bone marrow cells, reduction in the lymphocyte count, reduction in the neutrophil count, reduction in the white cell count, reduction in the platelet count and reduction in the CD4 lymphocyte count, as described in Common Terminology Criteria for Adverse Events V.4.0.

ii. When grade 1 pneumonitis (interstitial pneumonia) is observed.

iii. When the administration of the following cycle cannot be initiated by day 43 after the final dosing day of the previous cycle (considering the day following the final dosing day is day 1) due to an adverse event (the same day of the week, 6 weeks after the final dosing day will be accepted).

iv. When the physician-in-charge judges that the discontinuation of the protocol treatment is necessary due to an adverse event other than the criteria for treatment change.

3. When the patient requests the discontinuation of the protocol treatment because its association with an adverse event cannot be ruled out (this category will be applied when the association with the adverse event cannot be ruled out).

4. When the patient requests the discontinuation of the protocol treatment due to a reason for which the association with an adverse event can be ruled out (this category will be applied only when the association with an adverse event can be first ruled out, such as the moving of the patient or his/her family).

5. Death during the protocol treatment (death before the discontinuation of the protocol treatment due to another reason).

6. When the patient notifies the withdrawal of consent.

7. Other conditions, such as the aggravation of the condition after registration but before treatment initiation (protocol treatment cannot be initiated due to rapid aggravation), discovery of protocol violation and treatment change due to ineligibility as clarified by changes in the pathological diagnosis after registration. The date of death in the case of (5), and the day on which the physician-in-charge decides the discontinuation of the protocol treatment in the other cases will be regarded as the date of discontinuation of the protocol treatment.

Allocation procedure

The participants will be allocated to the groups using the electronic data capture (EDC) system. The EDC system will confirm the eligibility of the participants based on the registered information, and randomly allocate them to the groups at a 1:1 ratio in the order of case registration.

Allocation method: minimisation method

Allocation adjustment factors: Institution, disease stage (III vs IV/recurrence) and CA19-9 (≤1000 IU/mL, >1000 IU/mL)

Data collection and monitoring

Data collection

Participants will be enrolled from 24 centres. EDC will be used. The principal investigator or a person appointed by the principal investigator will log in to the EDC system using strictly managed individual electronic signatures (ID and password), immediately input collected case information, and send it to the data centre. The transmitted electronic data will be regarded as a case report.

Monitoring

Central monitoring will be performed based on the data collected through the EDC system, and no facility visit monitoring will be performed as a rule. The facility concerned may be contacted, as needed, with regards to the confirmation of data and the addition and entry of missing data. Periodic monitoring will be performed twice a year.

Endpoints

Primary endpoint

Overall survival

This study will evaluate the efficacy of the study treatment with regards to the true endpoint of chemotherapy for solid cancer—overall survival. Since there are no reliable data on the historical or control distant outcomes of pancreatic cancer chemotherapy for elderly patients, the outcome of the standard treatment in the randomly allocated participants will be secured. The objective of this study is to investigate whether the distant outcomes of patients aged ≥75 years, treated with GS therapy (n=40)/GEM therapy (n=33) in the large-scale randomised study (GEST study) in comparison with the corresponding outcomes of those treated with GEM therapy alone, as represented by the median overall survival of 9.8 vs 7.8 months, respectively (Taiho Pharmaceutical Co, Ltd, unpublished data) can be reproduced in a prospective study involving a large number of cases.

Secondary endpoints

1. Incidences of adverse events
2. Incidences of serious adverse events
3. Progression-free survival
4. Response rate

Statistical analysis

Analysis population

The efficacy endpoint will be analysed in all the eligible cases, and the safety will be analysed in all the treated cases. The analysis populations are defined as follows:

All registered cases

Of those participants who register following the procedure, those remaining after the exclusion of overlapped
and erroneous registrations will be defined as ‘all registered cases’.

All eligible cases
The registered participants who remain after the exclusion of ‘ineligible (ineligible after registration and at the time of registration, and violated registration) cases’, as decided by group investigation, will be defined as ‘all eligible cases’. ‘Ineligible cases’, as judged by only the physician-in-charge, coordinator and investigator of the institution, will be included in the ‘all eligible cases’ group. Cases judged as being ineligible only by central pathological diagnoses will not be regarded as ineligible and will be included in the ‘all eligible cases’ category.

All treated cases
Of all the registered cases, those receiving the study treatment, either partially or entirely, will be defined as ‘all treated cases’.

Analytical items and methods
The main analysis of this study is the final analysis, and the main objective is to identify whether GS therapy is an appropriate regimen as a study treatment in the phase III study.

In the main analysis, the primary endpoint—overall survival—will be analysed in all eligible cases by the estimation of the cumulative survival curve, MST and monthly survival rate, using the Kaplan-Meier method.

No statistical analyses will be performed in this study. In addition, analyses involving all registered cases will also be performed as a reference.

More attention will be paid to the following conditions in order to conclude that GS therapy is appropriate as a study treatment in the following phase III study. When any of the conditions are not met, determination will be comprehensively made.

► The 6-month and 12-month survival rates in group B are better than those in group A.
► The incidences of haematotoxicity of grade 3 or higher, and grade 2 or higher in group B are not higher by ≥10% compared with those in group A.

The draft conclusion will be prepared in consultation with the study management committee, and finally decided on through approval from the data and safety monitoring committee.

Interim analysis
No interim analysis will be performed.

ETHICS AND DISSEMINATION

Ethics
Written informed consent will be obtained from every patient prior to participation in the study.

Patient safety
Of the participants with adverse events of grade four or higher, those not meeting the terms stated in table 3 will be specified to be immediately reported.

DISCUSSION
This is an exploratory study to investigate the feasibility of GS therapy for elderly patients with pancreatic cancer, as a study treatment in the following phase III study. This study will clarify whether GS therapy is a candidate as a safe and effective new standard treatment, which can be administered at a reasonable cost, for the increasing proportion of elderly patients with pancreatic cancer.

Efficacy and safety data are available for patients with pancreatic cancer aged between 75 and 80 years old (Taiho Pharmaceutical Co, Ltd, unpublished data) in the subgroup analysis of the large-scale randomised

Table 3  Adverse events not specified for immediate reporting

<table>
<thead>
<tr>
<th>System organ class (CTCAE V.4.0)</th>
<th>Adverse event term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorders of the blood and lymphocytes</td>
<td>Anaemia and reduction in the number of bone marrow cells</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>Constipation</td>
</tr>
<tr>
<td>Systemic disorder and local symptoms</td>
<td>Fever</td>
</tr>
<tr>
<td>Infection and parasitic disease</td>
<td>Viral hepatitis</td>
</tr>
<tr>
<td>Laboratory test</td>
<td>Increase in alkaline phosphatase level, reduction in CD4 lymphocyte level, increase in cholesterol level, increase in GGT level, increase in lipase level, reduction in lymphocyte count, reduction in neutrophil count, reduction in platelet count, increase in serum amylase level and reduction in white cell count</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td>Obesity, anorexia, hyperuricaemia and hypoalbuminaemia</td>
</tr>
<tr>
<td>Musculoskeletal system and connective tissue disorders</td>
<td>Deep connective tissue fibrosis and superficial soft tissue fibrosis</td>
</tr>
<tr>
<td>Renal and urinary tract disorders</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Respiratory, thorax and mediastinal disorders</td>
<td>Paranasal disorder and sleep apnoea</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Hypohidrosis</td>
</tr>
</tbody>
</table>

GGT, gamma glutamyl transferase.
controlled study (GEST study) conducted in Japan. The data suggested that GS therapy is a promising candidate as a study treatment for elderly patients with pancreatic cancer (75–80 years old). However, there are no efficacy or safety data for elderly patients with pancreatic cancer aged ≥80 years. Thus, this randomised controlled study, by comparing GS therapy with GEM therapy alone, will be an important screening tool to decide on the progression to the following phase confirmatory study.

Contributors HI: prepared the study protocol, and will provide the final approval, perform an overview of the entire study through the study management committee and manage safety information. NY: will perform the statistical analyses. MU, SO and MS: will plan, investigate and manage the study. AMS: will support the preparation of the protocol and quality control (data management and monitoring).

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/ © Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES