treatment. In particular said treatment may comprise reduction in the size or volume of the CCA being treated. The treatment may include effects on the CCA closest to the optical fiber as well as other CCAs which are more distant and may not directly receive irradiation from the light source. In one example of the disclosure the method treats one or more cholangiocarcinoma (or cells therefore) which are not irradiated during the irradiation step (this includes direct or indirect irradiation, i.e. which do not receive a light dose resulting from the irradiation step).

A “cholangiocarcinoma” is a bile duct cancer which may be intrahepatic or extrahepatic (which may be perihilar and distal). Over 90% of CCAs are adenocarcinomas.

The “patient” is a human.

“Systemic administration” includes any form of non-local administration in which the agent is administered to the body at a site other than directly adjacent to, or in the local vicinity of, the CCA, resulting in the whole body receiving the administered agent. Conveniently, systemic administration may be via enteral delivery (e.g. oral) or parenteral delivery (e.g. intravenous, intramuscular or subcutaneous). Intravenous delivery is preferred.

“$TPCS_{2a}$“ is a photosensitizing agent (tetraphenyl chlorin disulphonic acid) having the structure below or isomers thereof. The structure below provides the 7,8-dihydro isomer. The 12,13- and 17,18-dihydro isomers are encompassed by the term $TPCS_{2a}$. Pharmaceutically acceptable salts thereof are also encompassed. Such molecules are as described in WO03/020309 and WO2011/018635 which are incorporated herein by reference.

advantageous. In the unit “J per cm” the cm is the length of the optical fiber if light is emitted over a length of the fiber (e.g. when a diffuser is used). In the alternative this may be cm of tumour, e.g. when a point light source is used. In both cases J/cm refers to the light dose provided per cm to the local environment. Conveniently the light dose is achieved using a light diffuser with a fluence of 100mW per cm of fiber (e.g. diffuser) and hence an irradiation time of from 2.5 to 10 minutes. Preferably a dose of 10 to 45 (or 15 to 45), e.g. 20 to 40 or 25 to 35 J/cm is used.

Furthermore, if cell viability is to be maintained, the generation of excessive levels of toxic species is to be avoided and the relevant parameters may be adjusted accordingly.

The methods of the disclosure may inevitably give rise to some cell damage by virtue of the photochemical treatment i.e. by photodynamic therapy effects through the generation of toxic species on activation of the photosensitizing agent. As the role of the method of the disclosure is to destroy tumour cells, this cell death may not be of consequence and may indeed be advantageous. In some examples, however, cell death should be avoided to ensure that the cytotoxic molecules are taken up into the cells to ensure localized and specific cell death. The methods of the disclosure may be modified such that the fraction or proportion of the surviving cells is regulated by selecting the light dose in relation to the dose (concentration) of the photosensitizing agent. Again, such techniques are known in the art.

Preferably, substantially all of the cells, or a significant majority (e.g. at least 75%, more preferably at least 80, 85, 90 or 95% of the cells) are not killed by the photochemical internalization method alone (i.e. without a cytotoxic agent). *In vitro* cell viability following PCI treatment can be measured by standard techniques known in the art such as the MTS test. *In vivo* cell death of one or more cell types may be assessed within a 1cm radius of the point of administration (or at a certain depth of tissue), e.g. by microscopy or other appropriate means. As cell death may not occur instantly, the % cell death refers to the percent of cells which remain viable within a few hours of irradiation (e.g. up to 4 hours after irradiation) but preferably refers to the % viable cells 4 or more hours after irradiation.

two (or more) preparations administration at the same time but via different intravenous entry points). When administered separately they may be administered at the same time or sequentially and/or may overlap in their administration timing. When used sequentially the time separating administration of the different agents is not more than 24 hours. Conveniently they are administered together in a single mixture.

In preferred features of the disclosure the gemcitabine and/or another cytotoxic agent used in step iii) is administered more than once, e.g. 2, 3, 4, 5, 6, 7, 8, 9 or 10 times (e.g. up to 20 times). This administration may be in a single (or each) cycle or in total in multiple cycles.

As referred to herein a “cycle” is a time period over which a particular treatment regime is applied and is generally repeated to provide cyclical treatment. The treatment in each cycle may be the same or different (e.g. different dosages, timings etc. may be used). A cycle may be from 14-30 days in length, e.g. a 21 day cycle. Multiple cycles may be used, e.g. at least 2, 3, 4 or 5 cycles, e.g. 6, 7, 8, 9 or 10 (e.g. up to 8, 9, 10 or 20) cycles. Within each cycle the gemcitabine and/or another cytotoxic agent may be administered once or more than once, as described hereinbefore. In a preferred feature the gemcitabine and/or another cytotoxic agent is administered twice in each cycle and preferably at last 3, preferably at least 5 cycles are conducted.

Whilst in a preferred feature the above step iii) treatment with gemcitabine and/or another cytotoxic agent is performed, in another example of the disclosure such treatment is not performed and in particular the treatment does not include the use of another cytotoxic agent such as cisplatin.

For effective treatment, the method described herein, or a part thereof, may be repeated. Thus, for example, steps i) and ii) may be repeated one or more times, e.g. 2 or 3 times, for example after an interval of from 1 to 6 months or longer, e.g. after step ii) or iii). In a preferred example the entire method is repeated at least twice, e.g. 3 or 4 times.

In a particularly preferred example the method comprises performance of the method twice (i.e. performance of steps i), ii), iii), i), ii) and iii)) or more, preferably in which in the first and/or second (or later) round of steps i) to iii), step iii) is performed at least twice. Thus by way of example, the method may be performed as follows:

i) systemically administering $TPCS_{2a}$ to said patient to a dose of 0.05 to 0.5 mg/kg (or 0.1 to 0.5 mg/kg) and

ii) after 3-5 days, systemically administering gemcitabine to a dose of 500-1500 $mg/m^2$ and 2-4 hours after completion of the gemcitabine administration irradiating said cholangiocarcinoma with light with a wavelength of 640-665nm using an optical fiber placed within 3cm of said cholangiocarcinoma to provide a light dose of 10 to 60 J/cm (or 15 to 60 J/cm);

iii) after 1-40 days (preferably after 7-21 days) systemically administering gemcitabine and/or another cytotoxic agent, preferably cisplatin;

iv) repeating step iii) at least once; and

v) repeating steps i) to iv) at least once.

In a particularly preferred example, step iii) is performed in cycles as described hereinbefore, in particular multiple cycles of step iii) are performed (before commencing to step iv)) and in each of these cycles the gemcitabine and/or another cytotoxic agent such as cisplatin is administered twice or more.

By way of example the method may be performed in which step iii) in the first and second round comprises 2, 3 or 4 cycles of gemcitabine and cisplatin administered once or twice, e.g. at days 1 and 8. When steps i) and ii) are performed after the first round step iii) and before the second round step iii), it may impinge on the first cycle in step iii) of the second round, e.g. the gemcitabine administration and irradiation may replace the first administration of gemcitabine and cisplatin in the first cycle. In one option, the patient is not subjected to any treatment for a period of between 1 week to 4 weeks after the first round (of steps i), ii) and iii)) before the second round is commenced. In that case the treatment then resumes with steps i) and ii) as indicated above, followed by step iii). Preferred timings of the treatment and/or doses to be used are as described in the Examples.

Prior to treatment the patient to be treated may be subjected to biliary stenting to ensure adequate biliary drainage. The stent, which may be plastic or metal, is

placed into the bile duct using procedures known in the art. The latter may be kept in place during illumination whereas the former are removed during illumination and a new stent inserted after that procedure.

The above methods and preferred features thereof also apply to uses of the above described agents. Thus, in an alternative example the present disclosure provides gemcitabine and $TPCS_{2a}$ and optionally another cytotoxic agent, preferably cisplatin, for use in treating a cholangiocarcinoma in a human patient, wherein i) said $TPCS_{2a}$ is to be systemically administered to said patient to a dose of 0.05 to 0.5 mg/kg (or 0.1 to 0.5 mg/kg); and
ii) after 3-5 days, said gemcitabine is to be systemically administered to said patient to a dose of 500-1500 mg/$m^2$ and said cholangiocarcinoma is to be irradiated with light with a wavelength of 640-665nm using an optical fiber placed within 3cm of said cholangiocarcinoma to provide a light dose of 10 to 60 J/cm (or 15 to 60 J/cm) (e.g. of the fiber or tumour); and optionally
iii) after 1-40 days (preferably after 7-21 days) gemcitabine and/or another cytotoxic agent, preferably cisplatin, is to be systemically administered to said patient.

The above described definitions and preferred features are similarly applicable.

Disclosed is a kit comprising gemcitabine and $TPCS_{2a}$ and optionally another cytotoxic agent as defined hereinbefore, preferably for simultaneous, separate or sequential use to treat a cholangiocarcinoma in a patient, wherein preferably said use is as defined hereinbefore.

In another aspect, the present disclosure refers to use of gemcitabine and $TPCS_{2a}$ and optionally another cytotoxic agent as described herein, in the manufacture of a kit for simultaneous, separate or sequential treating a cholangiocarcinoma in a patient, wherein said use is as described herein.

Preferred examples according to the disclosure are as set out in the Examples in which one or more of the parameters or components used in the Examples may be used as preferred features of the methods described hereinbefore.

The invention will now be described in more detail in the following non-limiting Examples with reference to the following drawings in which:

**Figure 1** shows cytotoxicity after 72 hours gemcitabine exposure. Viability of the cell lines TFK-1 (A) and EGI-1 (B) were analysed by the MTT assay after 72 hours gemcitabine incubation as described under Materials and Methods in Example 1.

Claims:

1. Use of gemcitabine and $TPCS_{2a}$ and optionally another cytotoxic agent, preferably cisplatin, in the manufacture of a medicament for treating a cholangiocarcinoma in a human patient, wherein
i) said $TPCS_{2a}$ is to be systemically administered to said patient to a dose of 0.05 to 0.5 mg/kg; and
ii) after 3-5 days, said gemcitabine is to be systemically administered to said patient to a dose of 500-1500 mg/m$^2$ and said cholangiocarcinoma is to be irradiated with light with a wavelength of 640-665nm using an optical fiber placed within 3cm of said cholangiocarcinoma to provide a light dose of 10 to 60 J/cm; and optionally
iii) after 1-40 days (preferably after 7-21 days) gemcitabine and/or another cytotoxic agent, preferably cisplatin, is to be systemically administered to said patient.

2. The use of claim 1, wherein said $TPCS_{2a}$ is to be administered to a dose of 0.05 to 0.3 mg/kg, preferably 0.2 to 0.3 mg/kg.

3. The use of claim 1, wherein said $TPCS_{2a}$ is to be administered to a dose of 0.1 to 0.5 mg/kg.

4. The use of any one of claims 1 to 3, wherein said gemcitabine in step ii) is to be administered to a dose of 900-1100 mg/m$^2$.

5. The use of any one of claims 1 to 4, wherein said irradiation is to be performed within 4 hours of the start of gemcitabine administration.

6. The use of any one of claims 1 to 5, wherein the wavelength of said light is 652nm.

7. The use of any one of claims 1 to 6, wherein said light dose is 10 to 45 J/cm, preferably 25 to 35 J/cm.

8. The use of any one of claims 1 to 6, wherein said light dose is 15 to 60 J/cm.

9. The use of any one of claims 1 to 8, wherein in step iii) both gemcitabine and another cytotoxic agent, preferably cisplatin, are to be administered.

10. The use of any one of claims 1 to 9, wherein in step iii) the gemcitabine is to be administered to a dose of 500-1500 mg/m$^2$, preferably 900-1100 mg/m$^2$.

11. The use of any one of claims 1 to 10, wherein in step iii) the cytotoxic agent is cisplatin which is to be administered to a dose of 10-50 mg/m$^2$, preferably 20-30 mg/m$^2$.

12. The use of any one of claims 1 to 11, wherein in step iii) said gemcitabine and/or another cytotoxic agent, preferably cisplatin, is to be administered more than once.

13. The use of claim 12, wherein said gemcitabine and/or another cytotoxic agent, preferably cisplatin, is to be administered more than once (preferably twice) in a 14-30 day cycle that follows 1-40 days after steps i) and ii).

14. The use of claim 11 or 12, wherein said gemcitabine and/or another cytotoxic agent, preferably cisplatin, is to be administered once or more (preferably twice) in at least 3 14-30 day cycles, wherein said first 14-30 day cycle follows 1-40 days after steps i) and ii).

15. The use of claim 14, wherein said gemcitabine and/or another cytotoxic agent, preferably cisplatin, is to be administered once or more (preferably twice) in at least 5 14-30 day cycles.

16. The use of any one of claims 1 to 15, wherein steps (i), (ii) and (iii) are to be performed at least twice.

17. The use of claim 16, wherein in each round of steps (i), (iii) and (iii), step (iii) is to be performed at least twice.

18. The use of any one of claims 1 to 17, wherein the systemic administration of one or more of $TPCS_{2a}$, gemcitabine and another cytotoxic agent, preferably cisplatin, is to be intravenous.

19. The use of any one of claims 1 to 18, wherein cisplatin is not to be used in said treatment.

20. The use of any one of claims 1 to 19, wherein said another cytotoxic agent is cisplatin.

21. Use of gemcitabine and $TPCS_{2a}$ and optionally another cytotoxic agent as defined in any one of claims 1-4, 10 and 11, in the manufacture of a kit for simultaneous, separate or sequential treating a cholangiocarcinoma in a patient, wherein said use is as defined in any one of claims 1 to 20.