Chemosensitizer - Resistance breaker

Methadone – an effective resistance knockout drug for cancer treatment

Main indication areas

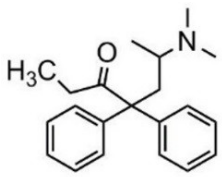
- **Usable for many different types of cancer like:** prostate cancer, hormonresistant prostate cancer, glioblastoma, pancreatic cancer, ovarian cancer, cisplatin-resistent ovarian carcinoma, HER2-resistent breast cancer, glioblastoma, glioblastoma stem cell, colon cancer, leukemia (ALL, AML, CLL), doxorubicin-resistant-leukemias, fludarabine- resistant CLL, liver cancer, liver metastases, non-Hodgkin-lymphoma, bladder cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, peritoneal carcinomatosis.

Positive factors influencing the market potential

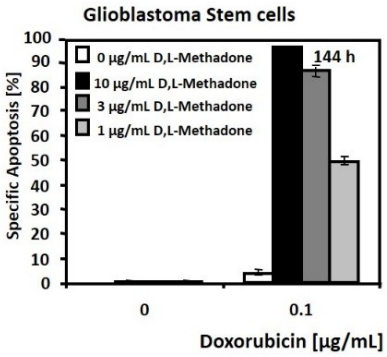
- Combinable with conventional therapies (overcoming resistance, more effective => lower doses of chemotherapeutica possible, longer treatment periods)
- Enhancement of activity in many chemotherapeutic classes such as anthracyclines such as doxorubicin, platin metal complexes such as oxaliplatin, cisplatin, carboplatin, topoisomerase inhibitors such as etoposide, purine analoga such as fludarabine
- Capable of long-term medication
- Limited registration and development costs, substance already approved for other indications, orphan-drug admission process possible
- Bioavailability, pharmacology well known
- Known therapy dose corridor
- Quick to bring into the market (nearly immediately)
- Results based on human-cell lines, patient cells, animal experiments, patient observations and experiences
- Published in high impact journals and invited presentations at medical societies

Technology

Opioids, a chemically heterogeneous group of substances are substances that bind as ligands to opioid receptors. Various tumor entitities such as breast cancer cells, neuroblastoma cells, bladder cancer cells, colon carcinoma cells, lung carcinoma cells, leukemia cells, glioblastoma cells, etc. overexpress strongly opioid receptors on their surface which is used as a characteristic for treatment specificity. Opioid receptors and their ligands may thus be used as a target for tumor therapy. Methadone is a pure μ-opioid receptor agonist. In vitro and in vivo studies of Friesen et al. shows that opioid receptor activation using the opioid receptor agonist D,L-methadone destroys tumor cells and sensitizes tumor cells for anti-cancer drug treatment. The sensitization is carried out via the μ–opioid receptor signaling pathway. Opioid receptor agonists triggering opioid receptors can activate inhibitory Gi proteins, which, in turn, block adenylyl cyclase activity reducing cAMP, which is involved in modulation of various signaling pathways. Activation of opioid receptors by D,L-methadone reducing cAMP level sensitizes conventional therapies forcancer treatment and reverses deficient activation of apoptotic signaling pathways in cancer cells. The enhanced toxicity for cancer cells of a combination treatment with D,L- methadone and anti-cancer drugs is associated with the upregulation of opioid receptor expression mediated by anti-cancer drugs and furthermore with an increased uptake and decreased efflux of anti-cancer drugs mediated by D,L-methadone.This was demonstrated using several human cancer cell lines and cancer patient cells such as leukemia, ovarian cancer, pancreatic cancer, breast cancer, prostate cancer and glioblastoma.



Methadone



D,L-Methadone sensitizes untreatable tumor stem cells for anticancer treatment Glioblastoma stem cells (right) treated with 0.1 µg/mL doxorubicin alone (white bars) or with different concentrations of D,L-methadone in combination with 0.1 µg/mL doxorubicin (right, black bars, dark gray bars, light gray bars). Treatment without doxorubicin (0 µg/mL) is shown with no specific apoptosis.

Patient case

Diagnose: Sigma stenosing carcinoma with primary peritoneal and pulmonary metastasis
Strong progression under the conventional therapies. Patient developed metastases (liver metastases, lung and bone filiae) during and after pantiumumab therapies and FOLFOX regimens. By addition of methadone, strong treatment response could be observed. The liver metastases were strongly reduced by combination treatment with methadone and panitumumab /irinodecan.
Only with methadone a treatment response was observed in this patient.
This observation was found in many patient cases.

Patent Status

- Patents granted in part (monopoly), filed in all industrialized countries (DE, EP, U.S., JP, Brazil, Russia, India, China etc.)
- Patent protection until 2028 to 2032 possible

Patent applications:

- USE OF OPIOIDS OR OPIOID MIMETICS FOR THE TREATMENT OF RESISTANT CANCER PATIENTSEP20080013741 20080731, EP2149372 (B1); JP2011529454 (A), RU2011107280 (A), CA2732497 (A1), CN102159212 (A), US2011270011; WO2010012319, In645/CHENP/201
- COMBINATION OF OPIOIDS AND ANTICANCER DRUGS FOR CANCER TREATMENT WO/2014/056897, EP2716291

Reference Number

UEE20120404Methadon

Status: Oct.-14

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