Biliary track carcinoma, chemotherapy and iREM

The unusual course of illness of a patient with a biliary track carcinoma (BTC) in stage IVb (ESMO Guidelines) should not remain without discussion. Since the patient was concomitantly treated with iREM as well for approx. one year, in addition to standard chemotherapy with gemcitabine/cis-platin regiment.

According to literature*, mPFS of BTC in advanced stages comes up to an average of 6.9 and 8 months with gemcitabine/platinum-based protocol, and the median overall survival (mOS) is between 9.7 and 9.85 months.

As evidenced by the findings below, our patient revealed signs of tumor progression not earlier than 14 months from the beginning of chemotherapy. Presently, 20 months later, the patient still enjoys good health. Thus, not only the overall survival (OS) significantly differs from that of other patients suffering from BTC, but also the duration of progression free survival (PFS) is significantly prolonged (that is the point of time from when the disease begins to progress again in spite of therapy). This is definitely worth mentioning.

Considering both the course of the disease, and the medical literature regarding BTC, everybody is free to assess whether this result may be attributed to the gemcitabine / cis-platinum containing chemotherapy only, or whether it is possibly due to iREM effect as well.

Some extracts from the patient’s records:

- **June 2014**: A hepatic mass of ca. 6 cm diameter was detected in segments VII / VIII in CT scan. Patient’s tumor was initially regarded as a hepatic manifestation of an adenocarcinoma of a CUP syndrome due to histo-pathologic examination of biopsies: A focal necrotic adenocarcinoma, G2, CK7-positive, TDF1-negative, CDX2 / PSA-negative; only few cell aggregates are CK20 positive.

- **July 2014** and **November 2014**: 2x TACE were performed. Follow-up CT (May 2015) revealed s/p tumor embolization; compared to previous examination, a progression of tumor size from 5 cm diameter to 6 cm was observed.

- **05/2015**: In an other hospital a hemihepatectomy right with anatomic resection of liver segment 4a and atypical resection in the area of the liver segment 1 was carried out. Pathologic finding: pT2b, L0 V0 Pn0; G3, locally R0 resection. Immune histochemistry: tumor strongly proliferating, carcinoma cells are positive for CA 19-9, IMP3, p53, CK7 and CK20 but negative for AFP and Hep par >> cholangiocellular carcinoma i. e. BTC.

Personal engagement of the patient made it possible to supply us with a small sample of the vital tumor. After short cultivation, the cells were frozen for cryopreservation.
- **MRT on September 15, 2015** (only relevant passages): suspect mass in segment 4a, ascites as well as small nodular lesions in the peritoneal fat tissue (DD postoperative alterations).

- **September 2015**: Admission of patient to the hospital for ascites drain. Approx 8.5l hemorrhagic ascites were drained. Diagnosis: Peritoneal carcinomatosis with ascites; cytoblock examination revealed many tumor cell clusters that are well compatible with peritoneal seeding of the known cholangiocellular carcinoma. Tumor marker CA 19-9 56.4 U/mL, AFP 5096 ng/ml.

  In order not to come into conflict with ethical principles, the patient was recommended a treatment with standard agents.

- **Oct. 20, 2015**: Initiation of systemic chemotherapy with gemcitabine (1000 mg/sqm BSA iv) and cisplatin (25 mg/sqm BSA iv) on day 1 and 8, to be repeated every 22 days.

  After the first cycle, the patient expressed his suicidality and insisted on a trial with IREM. Subsequently, in order to protect the immune cells from harmful effects of cytostatic agents, the taking of blood samples and re-injection of primed cells were carefully timed. Blood for leukocyte extraction was always taken on the day before applying the next course, and the trained leukocytes were administered 6-7 days after the last cytostatics application. The first iREM cells were administered mid November 2015.

- 3 **cycles** of the above mentioned chemotherapy were performed until Dec. 15, 2015. An improvement of disease could radiologically and clinically be observed in the sense of declining ascites and declining size of peritoneal metastases. Tumor markers also went down: AFP 462 ng/ml, CA19-9 120 U/ml.

- **CT Thorax and abdomen with contrasting agent on Dec. 21, 2015** (relevant passages):

  Roundish configured axillary and mediastinal lymph nodes increased in number and size (left axillary with approximately 1.0x1.3 cm (image 19) or approximately 0.8x1.2 cm in the pericardial fat tissue (image 48). Sharply edged hypodense lesions up to 0.7 cm in the remaining liver segment, constant in size (example image 53, previous examination (PE) image 56). Ascites significantly reduced. Furthermore, residual findings could be detected both perisplenically, and along the ascending colon, and in the bed of the resected right hepatic lobe (for example image 63 and image 74). Slightly decreasing of metastatic tissue ("omentum cake") along the ventral omentum (ca.3.79x6.6 cm in image 59, in contrast, 3.9x7.6 cm in image 60 of previous scan). Multiple lymph nodes and/or nodular, mesenteric, and retroperitoneal tissue formations, also decreasing in size (e. g. ca.3.3x1.8 cm in image 70, in contrast 4.2x2.5 cm in PE image 74).

- The ninth chemotherapy was in early May 2016. Restaging examination was carried out on May 18, 2016. Discontinuation of Chemotherapy was decided (June 2016).

- **CT Thorax and abdomen with contrasting agent on July 18, 2016** (relevant passages):

  No pathologically enlarged axillary, mediastinal or hilar lymph nodes were detected. The known peritoneal carcinomatosis is unchanged, and the streaky, nodular densities of greater omentum can't be measured with certainty. Still mesenteric lymph nodes smaller than 1 cm diameter are detectable.

  iREM treatment was continued 1-2 times a month until end of July 2016. The treatment was then discontinued for a certain time.
- **August 24, 2016:** After 9 cycles of chemotherapy, the patient introduced himself to a restaging examination on July 17, 2016. CT scan and laboratory tests showed a stable disease. Fall of tumor marker CA 19-9 (33 U/ml) continued, but a slight rise of tumor markers AFP (60 ng/ml) was observed. The findings were discussed with the patient. An extension of chemotherapy was decided for another two months. The next follow up examination was scheduled for September 19, 2016.

The last two courses of iREM were carried out in November 2016. The treatment had then to be ceased because the tumor cells necessary for modification had all been consumed.

- **CT Thorax and abdomen with contrasting agent on Jan. 24, 2017** (relevant passages):

  **Thorax:** Two lymph nodes in the right axilla are progradient in size with a short diameter of 0.9 and 0.8 cm (images 21 and 22, PE 0.5 cm, images 17 and 19). In the left axilla, several prominent but non-pathologically enlarged lymph nodes can be seen (e.g. image 22). Partly enlarged, partly constant lymph nodes in the anterior mediastinum, e.g. in the pre-cardiac adipose tissue 1.1 cm (image 46, image 44). A pretracheal lymph node constant in size of 0.8 cm (image 24, image 22). No suspiciously enlarged hilary lymph nodes. No pericardial or pleural effusion. No suspicious pulmonary masses.

  **Abdomen:** A faint roundish hypodense lesion in segment 1, 1.3x1.0 cm (image 14, PE 1.2 x 0.6 cm image 55) is progressive in its size. Several cystic lesions in the left hepatic lobe, e. g. image 8 (PE image 49). The streaky nodular formations in the omentum majus are also progredient (image 21; image 62), e.g. 1.1 x 1.6 cm (image 21, PE 1.0x0.8 cm image 61) or left subphrenic 0.9x1 cm (image 24, PE image 55). Some free liquid can be detected along the paracolic channel in either side. No suspiciously enlarged lymph nodes in iliakal or inguinal regions bilaterally.

- **CT Thorax and abdomen with contrasting agent on April 04, 2017** (relevant passages):

  **Thorax:** Unchanged enlarged lymph node right axillary, 1.8x1.1 cm (image 18, image 21). Lymph nodes constant in size in the pre-cardiac adipose tissue, 1.3x0.9 cm (image 47, image 46) and Arteria mammaia interna left, 0.8x0.7 cm. No pericardial effusion, no pleural effusion.

  **Abdomen:** Hypodense lesion in segment 1, regredient in size, 1.2 x 0.5 cm (image 58, PE 1.5x1.1 cm, image 14). Compared to December 13, 2016, the other hypodense lesions remained unchanged, most likely cysts. Constant nodules in the omentum majus, e. g. 1.5x1.0 cm (image 64, PE image 20) or left subphrenic, 1.0x1.0 cm (image 58, PE by 1.1x0.9 cm, image 13). No free liquid. No pathological lymphnodes iliical and inguinal.