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## Selected literature

### Part 1

#### Adjuvant treatment with capecitabine of breast cancer patients after failure of preoperative chemotherapy

The results of final analysis of the CREATE-X Phase III study were published in “New England Journal of Medicine” in June 2017. The study was designed to evaluate the efficacy of capecitabine in postoperative treatment in patients with HER2-negative breast cancer, who did not achieve complete pathological response after preoperative treatment (invasive lesions/lymph node metastases). The study included 910 patients with HER2-negative breast cancer (I to IIIB) with no complete pathological response after preoperative chemotherapy (95% of patients received anthracyclines given sequentially or concomitantly with taxanes, and 5% other chemotherapy regimens). Patients were randomly assigned 1:1 to 6–8 cycles of capecitabine (1250 mg/m<sup>2</sup> of body surface twice a day on days 1–14 every 21 days) or standard postoperative treatment. Initially six to eight cycles of chemotherapy were used during postoperative treatment, with most patients receiving eight cycles. Neoadjuvant chemotherapy included at least four cycles with anthracyclines. Standard postoperative treatment included hormone therapy and radiotherapy, depending on the indications.

Three year disease-free survival (DFS) rates were 82.8% and 73.9%, and five-year DFS rates 74.1% and 67.6% in the capecitabine and control groups, respectively, which translates into statistically significant reduction in relative risk of recurrence (relapse/second cancer/death) by 30% (HR = 0.70, p = 0.01). Three-year overall survival (OS) rates were 94.0% and 88.9%, and five-year rates 89.2% and 83.6% in the capecitabine and control groups, respectively, which translates into statistically significant reduction in relative risk of death by 41% (!) (HR = 0.59, p = 0.01). Subgroup analysis showed the greatest benefit from adjuvant treatment with capecitabine in patients with triple-negative breast cancer, with relative risk of death reduced by 48% (HR = 0.52, 95% CI 0.30–0.90).

Adverse reactions were typical for capecitabine, with palmar-plantar erythrodysesthesia (PPE) observed in

almost 75% of patients, including grade 3 PPE in 11% of patients.

#### Comment

We have known for a long time that obtaining a complete pathological response (pCR) to neoadjuvant treatment in breast cancer patients is an indicator of very good prognosis. On the other hand, the prognosis for complete cure in patients who have failed preoperative treatment (residual invasive cancer or metastatic lymph nodes in pathological examination) is still unfavourable. In adjuvant treatment of patients with HER2-positive or ER+ breast cancer, trastuzumab or hormone therapy are used, assuming that they could improve prognosis of patients who did not achieve pCR after classic neoadjuvant chemotherapy. Currently, for patients with triple-negative breast cancer, who did not receive pCR after full preoperative treatment, we do not have any options of adjuvant treatment. The final publication of the results of the CREATE-X study in the most important medical journal, the “New England Journal of Medicine”, is practically changing the standard of practice from today. Finally, we have an active therapeutic option with proven (IA) efficacy that decreases the relative risk of death by more than 40% and relative risk of recurrence by 30%. Adjuvant treatment with capecitabine should be routinely used in patients with triple-negative breast cancer after failure of preoperative chemotherapy, and in patients with luminal B subtype this treatment should be considered.

#### Source

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## Gemcitabine + capecitabine for adjuvant treatment of pancreatic cancer — full publication of ESPAC-4 results

The results of the ESPAC-4 study presented at ASCO meeting in June 2016 appeared in “The Lancet” in January 2017 as a full publication.

The ESPAC-4 study was a multicentre, open-label, randomised, controlled trial comparing gemcitabine in combination with capecitabine with gemcitabine alone for the adjuvant treatment of patients after macroscopically radical surgery (R0 or R1 resection) due to pancreatic adenocarcinoma. In total 732 patients in 92 hospitals in England, Scotland, Wales, Germany, France, and Sweden were included in the study between November 2008 and September 2014. Patients received gemcitabine 1000 mg/m<sup>2</sup> in intravenous infusion on days 1, 8, and 15 in combination with oral capecitabine at a daily dose of 1660 mg/m<sup>2</sup> on days 1–21 of a 28-day cycle (n = 349) or gemcitabine alone in the same pattern (n = 358) as adjuvant therapy. The treatment was administered for 24 weeks, i.e. six cycles. The primary endpoint of the study was overall survival. Secondary endpoints included: two-year and five-year survival rates and relapse-free survival.

The ESPAC-4 study showed statistically significant improvement of overall survival in the capecitabine plus gemcitabine arm [an increase in median OS by 2.5 months from 25.5 to 28 months; HR for OS 0.82 (95% CI 0.68–0.98), p = 0.032]. There was also an increase of the five-year survival rate by 12.5% (from 16.3% to 28.8%). The greatest benefit was observed in R0 patients. Median survival in patients after R0 resection was 39.5 months in the combination group versus 27.9 months in the gemcitabine alone group. In patients undergoing R1 resection these medians were 23.7 months (gemcitabine + capecitabine) and 23.0 months (gemcitabine), respectively. 12-month and 24-month survival rates were 84.1% and 53.8%, respectively, in the combination arm and 80.5% and 52.1% in the arm with gemcitabine alone. Toxicity during combination therapy was markedly higher, although manageable by means of recognised and available management methods. It did not have a significant negative impact on patients’ quality of life. According to the authors, the combination of gemcitabine and capecitabine should be the treatment of choice in patients after pancreatic cancer resection.

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### Comment

The results of the ESPAC-4 study have significantly altered the standard of care for postoperative patients with pancreatic adenocarcinoma and indicate a possible improvement of prognosis. Significant efficacy of postoperative combined chemotherapy is reported primarily in patients after microscopically radical resection (R0). This observation confirms the importance of good qualification of patients and of conducting surgical treatment in specialised, extensively experienced surgical centres. Since September 2016 capecitabine has been reimbursed in combination with gemcitabine in the postoperative treatment of patients with pancreatic adenocarcinoma within the chemotherapy catalogue.

### Sources

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## New standard of zoledronic acid use in patients with bone metastases from solid tumours

In January 2017 “JAMA” and “JAMA Oncology” published the results of two randomised clinical trials evaluating the efficacy of a new zoledronic acid (ZOL) treatment regimen in patients with bone metastases from cancers. For many years, administration of ZOL

every 3–4 weeks has been well established as a prophylaxis of skeletal related events (SRE) in patients with advanced solid tumours with bone lesions, which is according to a registered label. ZOL given every 3–4 weeks reduces pain and decreases the incidence of

SRE including fractures, spinal cord compression, and the need for surgery or irradiation by 25 to 40%. Zoledronic acid, a bisphosphonate of the third generation, similarly to other bisphosphonates, has side effects, of which osteonecrosis of the jaw, impaired renal function, and hypocalcaemia are the most serious. For many years the possibility of administering this drug at longer intervals has been considered. Recently published results of clinical trials concern a new regimen for the use of this drug, i.e. three-month intervals instead of four weeks. The results of these studies confirm the initial observations regarding the possibility of reducing the frequency of zoledronic acid infusions as part of SRE prophylaxis in the ZOOM study published in “The Lancet” in 2013 and endorse the new standard of SRE prophylaxis in patients with bone metastases in the course of advanced cancer based on administration of zoledronic acid with three-month intervals.

The study published by Himmelstein et al. answers the question of whether the use of ZOL in patients with bone metastases due to solid tumours in a three-month regimen for two years was no less effective than ZOL administered every four weeks. In an open-label, randomised study 1822 patients participated with generalised breast cancer (n = 855), prostate cancer (n = 689), and multiple myeloma (n = 278), with a median age of 65 years. In total 795 patients completed the study; in 29.5% of patients receiving ZOL every four weeks and 28.6% of patients receiving ZOL every 12 weeks at least one SRE occurred within two years after randomisation. The SRE ratio did not significantly differ between the two study groups, and the pain index, performance parameters, incidence of osteonecrosis, and renal dysfunction also did not differ significantly between groups. The mortality rate due to bone complications was similar in both groups; however, the so-called bone turnover (expressed as C-terminal telopeptide concentration) was higher in the group receiving ZOL every three months.

The prospective, multicentre, double-blind, phase III, randomised clinical trial OPTIMIZE-2 was designed to compare efficacy of ZOL used at 4- and 12-week intervals for one year. The study involved 416 patients (median age 59.2 years) with bone metastases due to breast cancer, who had previously received at least

nine doses of zoledronic acid or pamidronic acid within 10–15 months. In total 203 patients received ZOL every 12 weeks, 200 patients received ZOL every four weeks, and 13 patients received placebo. After a one-year follow-up period, the incidence of SRE in both groups was not significantly different (22.0% in the group receiving ZOL every four weeks *versus* 23.2% in the group receiving ZOL every 12 weeks), similarly to time to first SRE occurrence (HR 1.06; 95% CI, 0.70–1.60; p = 0.79). The mortality rate associated with bone complications was 0.46 in a group receiving ZOL every four weeks and 0.5 in a group receiving ZOL every 12 weeks, respectively. The safety profile of ZOL in both groups was similar, 95.5% of patients in a group receiving ZOL every four weeks had at least one adverse event (n = 189), and in a group receiving ZOL every 12 weeks it was 93.5% (n = 189).

## Comment

Published results of clinical trials confirm that the efficacy of zoledronic acid administered at 12-week intervals is no less than the efficacy of this drug at four-week intervals, with comparable tolerability and safety profile. These observations should serve as a basis for changing the current ZOL use standard regimen with intervals of 3–4 weeks to a schedule with 12-week intervals.

## Sources

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## Pembrolizumab in second-line treatment of patients with bladder cancer — a significant improvement of overall survival and a positive impact on quality of life (phase 3 KEYNOTE-045 study)

Advanced transitional cell carcinoma (TCC) remains a malignancy of poor prognosis and treatment options in subsequent lines, after exhaustion of efficiency of first-line platinum-based regimens, are limited. The

results of the phase 3 KEYNOTE-045 study published in “New England Journal of Medicine” in February 2017 show improvement of prognosis in patients treated with pembrolizumab.

The KEYNOTE-045 (NCT02256436) study was an open, international phase III randomised clinical trial, involving patients with advanced urothelial cancer with recurrence or progression of disease following prior platinum-based chemotherapy (n = 542). Patients were randomly assigned to receive pembrolizumab 200 mg every three weeks (n = 270) or chemotherapy with paclitaxel (175 mg/m<sup>2</sup>), docetaxel (75 mg/m<sup>2</sup>), or vinflunine (320 mg/m<sup>2</sup>) every three weeks (n = 272) based on investigator choice. Primary endpoints of the study were overall survival (OS) and progression-free survival (PFS), assessed in the whole group and among patients with PD-L1-positive tumours (at least 10%; the ratio of PD-L1-positive tumour cells and infiltrating immune cells to all cells in the tumour was assessed). Secondary endpoints were objective response rate, duration of response, and safety.

In the total study population (regardless of PD-L1 expression level) the use of pembrolizumab was associated with a significant reduction of relative risk of death by 27% (median OS: 10.3 months for pembrolizumab *versus* 7.4 months for chemotherapy; HR = 0.73; p = 0.002). In the PD-L1-positive population the use of pembrolizumab was associated with a reduction of relative risk of death by 43% (median OS: 8.0 months for pembrolizumab *versus* 5.2 months for chemotherapy, HR = 0.57, p = 0.005). The use of immunotherapy resulted in significantly higher objective response rate (21.1% *vs.* 11.4%; p = 0.001). There were no significant differences in progression-free survival between the study and control groups.

Immunotherapy was better tolerated than chemotherapy. At least one adverse event was observed in 60.9% of patients undergoing immunotherapy and 90.2% of patients receiving chemotherapy, and severe adverse events occurred in 15% and 50% of patients, respectively. The most frequently observed adverse events related to immunotherapy (of any grade of intensity) include pruritus (in 19.5% of patients), fatigue (13.9%), and nausea (10.9%).

During the 2017 Genitourinary Cancers Symposium in Orlando, the results of the KEYNOTE-045 study were

presented regarding patients' quality of life assessed using the EORTC QLQ-C30 questionnaire. At baseline the overall health status and quality of life were similar in both groups. In the pembrolizumab group the values were stable at up to 15 weeks of treatment, and in the chemotherapy group they deteriorated at the same time. Comparing to chemotherapy, use of pembrolizumab was associated with long-term maintenance of good quality of life.

## Comment

The results of KEYNOTE-045 study represent a breakthrough in second-line treatment of patients with advanced urothelial bladder cancer as such results confirm the significant improvement of prognosis by immunotherapy. In this study, pembrolizumab significantly prolonged overall survival compared to chemotherapy with a much better safety profile. As with other cancers, there was no significant effect of anti-PD1 immunotherapy on progression-free survival compared to standard treatment.

Currently, in the US three other drugs belonging to the group of checkpoint inhibitors are registered for the treatment of advanced bladder cancer patients: atezolizumab, durvalumab and nivolumab. They received FDA marketing authorisation based on the results of phase II studies. In 2017 EMA has approved pembrolizumab and nivolumab for second line treatment of urothelial bladder cancer.

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## ASCO and CCO recommendations on the use of bisphosphonates in the adjuvant treatment of patients with breast cancer

On 6 March 2017 the JCO published new evidence-based recommendations from the American Society for Clinical Oncology (ASCO) and CCO (Cancer Care Ontario) on the use of bisphosphonates and other bone turnover modulators for the adjuvant treatment of breast cancer patients, prepared by the authors based on a review of available literature.

Based on review, it was found that the use of bisphosphonates in adjuvant therapy reduces the risk of bone metastases and the risk of death from breast

cancer in postmenopausal patients. In almost all studies included in the review, patients received systemic treatment at the same time. It was noticed that the absolute benefit from using bone modulators is greatest in patients with a higher risk of recurrence. In most of the reviewed studies zoledronic or clodronic acid was used, so the data on the use of other bisphosphonates are very limited. Denosumab has been shown to reduce the risk of fractures, with no data on its impact on long-term survival.

According to the aforementioned guidelines for postmenopausal patients eligible for systemic adjuvant treatment after breast cancer surgery zoledronic acid should be considered, if possible, administered every six months or oral clodronic acid administered every day. The decision regarding implement this procedure should be based on a discussion with the patient about the potential benefits and risks and taking into account patient and disease characteristics, including recurrence risk. Prior to use of these drugs, the risk of osteonecrosis of mandible and/or maxilla and deterioration of kidney function should be assessed, and any changes in the oral cavity and changes requiring dental treatment should be cured before treatment.

## Comment

Meta-analysis, based on review of individual cases of more than 22,000 patients participating in seven clinical trials, published in “The Lancet” in 2015 has shown that the benefit of bisphosphonates in adjuvant therapy is independent of the bisphosphonate used (clodronic,

ibandronic, zoledronic acid). Considering the benefits from complementary use of bisphosphonate in postmenopausal breast cancer patients, including the reduction of risk of recurrence in bones, death from breast cancer, and the prevention of osteoporosis and its complications (including fractures), the use of this group of drugs seems justified. Taking all of the above data into account, the optimum, least debilitating form of bisphosphonate use appears to be either using 4 mg of zoledronic acid in intravenous infusions every six months for 3–5 years or oral clodronic acid 1600 mg daily for 2–3 years.

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## Thrombocytosis as a predictor of cancer — results of prospective cohort studies, published in “The British Journal of General Practice”

In May 2017 “The British Journal of General Practice” published the results of a prospective cohort study based on an analysis of available evidence from clinical practice from the years 2000–2013 regarding the risk of malignant neoplasia in people with thrombocytosis ( $> 400,000/\mu\text{L}$ ). The incidence of cancers within one year was compared in two groups: 40,000 patients at the age of at least 40 years with thrombocytosis and 10,000 patients with normal level of platelets. Additional analyses included the assessment of cancer risk according to gender, age, platelet count, and tumour location. In the published analysis, malignant disease was diagnosed in 11.6% of men with thrombocytosis (1098 out of 9435, 95% CI 11.0–12.3) and in 4.1% without thrombocytosis (106 out of 2599, 95% CI 3.4–4.9), and in 6.2% of women with thrombocytosis (1355 out of 21,826, 95% CI 5.9–6.5) and 2.2% without thrombocytosis (119 out of 5370, 95% CI 1.8–2.6). The risk of cancer increases to 18.1% in men and 10.1% in women if no further reduction in thrombocytosis is observed in a subsequent blood test after six months. In people with thrombocytosis, the most commonly diagnosed cancer is lung cancer and colorectal cancer. In one third of people with thrombocytosis who develop these cancers, there are no signs of active malignant disease.

## Comment

Thrombocytosis is a phenomenon often associated with advanced cancer, but its role as an early marker of

malignant disease has not been clearly proven to date. Based on a large, prospective population study, strong arguments have been obtained for increased oncological alertness in healthy subjects who experience thrombocytosis ( $> 400,000 \text{ PLT}/\mu\text{L}$ ) in routine laboratory tests, especially if the elevated values persist in subsequent test, performed after six months. Among men with thrombocytosis the incidence of lung cancer is clearly increased from 14% to 23% and colorectal cancer from 14% to 18% as well as cancers of upper gastrointestinal tract, as compared to the general population of men in the UK. Contrary to this, in women the incidence of colorectal cancer increases from 11% to 21%, and lung from 12% to 14%, as well as ovarian cancer. Prostate cancer and breast cancer are relatively less common in individuals with thrombocytosis than in the general population.

The results of this study should provide the basis for increased oncological alertness, especially for primary care physicians, and faster referral to prophylactic treatment of patients with thrombocytosis, especially if it persists for at least six months.

## Source

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## Correlation between obesity and morbidity and mortality due to cancer — a review published in “British Medical Journal” in February 2017

Obesity is becoming the biggest health problem in the world and is responsible for numerous serious diseases, including cardiovascular diseases and type 2 diabetes. Over the past 40 years the incidence of obesity worldwide has doubled in women and increased three-fold in men. An increasingly explored and discussed topic is the relationship between morbidity and mortality due to malignant neoplasms and obesity. Prevention and treatment of obesity can reduce not only the incidence and mortality rates of cardiovascular diseases or diabetes, but also of malignancies.

The authors reviewed 204 systematic reviews and meta-analyses dedicated to assessing the association between obesity and morbidity and mortality due to 36 malignancies. PubMed, Embase, and Cochrane databases were searched for meta-analyses and systematic reviews of the association between obesity-related parameters and development of cancers or death from malignant neoplasms using a previously prepared algorithm. The obesity parameters included body mass index (BMI), waist circumference, hip circumference, body weight, weight gain, and weight loss after bariatric surgery. In total 204 meta-analyses assessed the relationship between obesity parameters (mentioned above) and incidence ( $n = 196$ ) and mortality ( $n = 8$ ) due to cancers of 36 anatomical locations.

Based on the review, the authors noted that the relationship between obesity and the occurrence of various cancers has been investigated previously, with 11 of them being fully confirmed. They are primarily tumours of the gastrointestinal tract (GI) and hormone-related cancers in women. BMI increase was associated with a higher incidence of esophagogastric junction (EGJ) carcinoma, colon and rectal cancer in men, cancers of the biliary tract, pancreatic carcinoma, endometrial cancer in premenopausal women, renal-cell cancer, and myeloma. Weight gain and waist-to-hip circumfer-

ence ratio were associated with a higher risk of breast cancer in postmenopausal women who had never used hormone replacement therapy (HRT) and endometrial cancer. The increase in cancer risk for each weight gain by 5 kg/m<sup>2</sup> of BMI ranged from 9% (relative risk 1.09, 95% CI: 1.06–1.13) for rectal cancer in men to 56% (1.56, 95% CI 1.34–1.81) for biliary tract cancer. The risk of breast cancer in postmenopausal women who had never used HRT increased by 11% for every 5 kg of body weight gain during adulthood (1.11, 95% CI 1.09–1.13) and the risk of endometrial carcinoma by 21% for each increase in waist-to-hip circumference ratio by 0.1 (1.21, 95% CI 1.13–1.29). The other five links were supported by strong evidence for the use of specific methods of measuring obesity: weight gain with colorectal cancer, increased BMI with biliary tract cancer, gastric cardia, and ovarian cancer; and the association with mortality due to myeloma.

### Comment

Obesity and associated risks of other diseases are becoming a leading health problem worldwide. Evidence for the link between obesity and morbidity and mortality due to cancers may facilitate future screening of individuals at increased risk for morbidity/mortality, in whom implementation of primary and secondary prevention may be attempted. This knowledge also constitutes a strong argument in the fight against obesity, being an increasingly important health problem.

### Source

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