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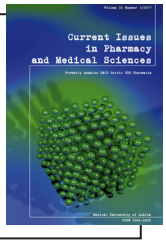

Systemic treatment of Krukenberg tumors

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ABSTRACT

Of all ovarian tumors with distinct biological features, 10-25% are secondary ovarian tumors. Among the most common cancers that cause ovarian metastasis are breast cancer, colorectal cancer, endometrium, as well as gastric and lateral cancer. Krukenberg tumors remain asymptomatic until the tumor reaches a certain size, as in the case of primary ovarian cancer. Symptoms are non-specific: abdominal pain (42%), postmenopausal bleeding (18%), weight loss (6%) and an increasing abdominal girth (15%). Diagnostic procedures should include physical examination, basic blood and biochemistry tests, radiographic imaging and endoscopy. There are currently no uniform guidelines to be followed in order to treat this cancer. However, the survival rate of selected subgroups of patients may be enhanced by means of cytoreductive surgery (performable among patients with good general health condition), where the metastases are limited only to the ovaries, where the primary tumor is derived from the colorectal cancer, and where there is the absence or minimal residual disease. It is still controversial to use adjuvant chemotherapy following the metastasectomy of Krukenberg tumors. Although this type of treatment seems to provide a survival benefit, there are currently no randomized prospective trials available so as to confirm or deny. Future research should, therefore, be focused on the potentially synergistic effect of surgery and perioperative administration of cytotoxic therapies targeted at high response rates. Studies on new molecularly targeted drugs can also be beneficial.

A Krukenberg tumor is a metastatic adenocarcinoma of the primary lesion located in the gastrointestinal tract. In 76% of all cases it has a gastric origin [1,2], and in 80% of all cases it is bilateral. This cancer consists of ringed cells [1,3]; it spreads retrogradely through the lymph nodes and accounts for 1-2% of all ovarian tumors [1]. The recurrence of the Krukenberg tumor especially includes retroperitoneal lymph nodes [4]. It is more common among young women; the average age of patients being 45 years. Symptoms are similar to ovary involvement, such as pain and abdominal distension. In other cases, patients report non-specific gastrointestinal symptoms. The disease can also be asymptomatic. Ascites are also evident in 50% of all cases. Herein, the tumor cells are usually present in the peritoneal cavity fluid. Still, the primary tumor is usually too small to be detected with conventional imaging examinations, therefore, doctors do not feel forced to perform in-depth diagnostics through applying other tests. However, computed tomography (CT) or ultrasonography (USG) of the abdomen and pelvis usually does show the bilateral, solid tumor of the ovary; moreover, cystic lesions may also be present. Detection of primary tumors at the time of diagnosis of Krukenberg tumor is only at a rate of 25-30% of actual cancers. Prognosis is poor, with an average overall survival of 14 months and worse, especially when ovarian metastasis is detected after primary focus or when the primary tumor is not localized at all [1]. Patients with Krukenberg tumor of colorectal origin rather than those of gastric origin show better prognosis [2]. Optimal treatment has not been established, but research data shows potential efficacy when aggressive chemotherapy and surgery are applied [1,5]. Among patients who are candidates for surgery, the best options to increase survival rate are to perform a metastasectomy, followed by palliative chemotherapy for metachronous tumors, or by simultaneous resection of the primary tumor with metastasectomy, followed by palliative chemotherapy for synchronous tumors [6].

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Chemotherapy is the most appropriate strategy for the management of recurrent or metastatic gastric cancer, although there are no significant benefits in prolonging survival. Various treatment strategies have, thus, been investigated so as to improve overall survival (OS). Local treatments, including metastasectomy, radiofrequency ablation, and stereotactic radiotherapy, show promising results. In addition, prolongation of OS has been demonstrated in colorectal cancer with operable metastases via resection of liver and lung. Such results have contributed to changes in recommendations by the National Comprehensive Cancer Network (NCCN). However, clear benefits in OS have not been determined from metastasectomy as applied in gastric cancer with Krukenberg tumors, since, in most cases, they are metachronously diagnosed. Determining the best treatment strategy is still controversial [7].

Cho *et al.* [2015] compared the effectiveness of metastasectomy combined with chemotherapy, to chemotherapy among patients with advanced gastric cancer and with Krukenberg tumor. In their study, 216 patients were assigned to two groups according to the treatment method: Group A – metastasectomy + chemotherapy, and Group B – chemotherapy. OS was significantly higher in Group A than in Group B among patients with stage IV gastric cancer at the moment of diagnosis (18.0 months vs. 8.0 months, $p < 0.001$), and among patients with recurrent Krukenberg tumors (19.0 months vs. 9.0 months, $p = 0.002$), respectively. Their research also showed a prognostic significance of metastasectomy in OS (beneficial effects), pathological ringed cells (evidently as a poor prognosis) and tumor cells in peritoneal fluid (worse prognosis). Cho *et al.*, hence, recommend metastasectomy in the fourth stage of gastric cancer with a metachronously or synchronously diagnosed Krukenberg tumor, and underline the importance of surgical treatment combined with chemotherapy [7].

Adjuvant, platinum-based chemotherapy after cytoreductive surgery appear to provide enhanced survival among patients with gastric cancer and Krukenberg tumor. Some reports, however, indicate no difference in OS between intravenous and intraperitoneal adjuvant chemotherapy among basal gastric cancer patients who have had Krukenberg tumors surgically removed. However, other research demonstrate that a significantly longer OS was observed among patients who received a combination of hyperthermic intraperitoneal chemotherapy (HIPEC) and systemic chemotherapy, when compared to those who received systemic chemotherapy alone (33 *vs*. 20 months, $p = 0.0005$). Furthermore, most studies on the combination of 5-fluorouracil (5-FU) + leukovorin (LV) have shown benefits in progression-free survival (PFS), although no statistically significant effect on OS has been shown. What is more, better results appear to be provided by triple regimens in combination with oxaliplatin than by the 5-FU + LV alone. In contrast, regarding PFS, there is no evidence of successful association with irinotecan dual-mode regimens as applied in adjuvant therapy after the performed surgery for primary colon cancer [8].

Xu *et al.* [2017] included in their study, fifty-seven patients with documented diagnosis of malignant neoplasm of the colon, rectum or ovary as listed between 1994 and 2013 in the medical records of the Capital Medical University Cancer Centre and the Beijing Cancer Hospital. Their average survival time was 35 months, while five-year overall survival amounted to 25% of all cases. They noted significantly longer survival among the patients who had experienced recurrence within 2 years after primary tumor resection and had underwent complete cytoreduction, had metastatic disease limited to the pelvic region, with N0 and who had received systemic chemotherapy. This was in contrast to patients who had synchronous metastases ($p = 0.027$), were without complete cytoreduction ($p < 0.001$), had pelvic metastases ($p < 0.001$), had metastatic lymph node involvement ($p = 0.011$), and did not receive systemic chemotherapy ($p = 0.006$). All adjuvant schemes included fluorouracil. Two patients received bevacizumab for 4-6 cycles. All patients with peritoneal seeding were subject to early postoperative intraperitoneal chemotherapy with 5-fluorouracil, mitomycin, cisplatin, or irinotecan for 1 to 5 cycles. Significantly better prognosis was thus associated with a more limited metastatic disease, complete cytoreduction and systemic chemotherapy [9].

Brieau *et al.* [2016] evaluated the efficacy of new chemotherapy regimens in first-line treatment for patients with ovarian metastases from gastric cancer. In the retrospective study, thirty-five (median age – 50.5 years) subsequent patients with ovarian metastases from gastric cancer who received at least one chemotherapy course were included. In their study, 60% of the total had synchronous ovarian metastases, while 48.6% (or seventeen) underwent oophorectomy. First-line chemotherapy was based on platinum, irinotecan, taxane plus platinum or epirubicin plus platinum. The median PFS and OS were 6.8 and 18.8 months, respectively. What is more, there was no significant difference in objective response rate (ORR) among patients with extra-ovarian metastases (13.6%) and inter-ovarian metastases (20.9%) ($p = 0.55$). There was also no significant difference in terms of ORR on ovarian metastatic site according to the first-line chemotherapy ($p = 0.21$). Still, oophorectomy was an independent prognostic factor significantly linked to OS ($p < 0.01$). This study indicates that gastric cancer metastases to ovaries are not more resistant than extra-ovarian metastases [10].

Wu *et al.* [2015] enrolled a total of 128 patients in their study. At the moment of diagnosis of Krukenberg tumor, the median age was 48 years (range, 27-65 years). Herein, the most common primary tumors were located in the colon (58 patients, 45.31% of the total) and stomach (41 patients, 32.03% of the total). In this research, Krukenberg tumors were more common among premenopausal (75.78%) rather than postmenopausal women. Moreover, 92 patients out of 128 (71.87% of the total), had metachronous ovarian metastasis. The patients of this study were given the following treatment options: metastasectomy among 114 patients (89.06%) (herein, 14 patients (10.94%) did not actually undergo surgery due to additional metastatic lesions); chemotherapy among 89 patients (69.53%). The surgical treatments consisted of unilateral or bilateral adnexectomy and hysterectomy with bilateral adnexectomy. Chemotherapy included cisplatin, carboplatin, oxaliplatin, docetaxel and 5-fluorouracil. Most of the patients received chemotherapy regimens containing two or three drugs, usually for

4-6 cycles. The majority of patients (98 patients, 76.56%) had bilateral ovarian metastases, 63 patients (49.22%) had ascites, 71 patients (55.47%) had metastatic disease limited to the ovaries, while 57 patients (45.53%) had extra-ovarian metastases: in pelvis, bone, lung and other distant organs. The median OS was 16 months (ranged between 5 and 52 months). This research, just like the others, revealed that metastasectomy was a beneficial prognostic factor in terms of OS. Moreover, chemotherapy combined with surgery is also a more successful option. In this research, over two-thirds of the patients received chemotherapy. Herein, the majority of chemotherapy regimens was based on platinum agent plus 5-fluorouracil, the remaining patients received docetaxel and paclitaxel and had distinct survival benefits [11].

Uyeturk *et al.* [2013] enrolled 8 patients (0.45%) with histopathologically identified Krukenberg tumors, among 1755 patients diagnosed with gastric cancer in their study which occurred between January 2005 and January 2012 at the Ankara Oncology Education and Research Hospital. The median age was 42.2 years (range, 32-69 years). Furthermore, 7 (87.5%) were premenopausal, 1 (12.5%) was postmenopausal. The performance status was: ECOG 1 in 7 patients (87.5%), ECOG 2 in 1 patient (12.5%). Surgery was performed among 4 patients (50%): total gastrectomy among 2, and distal subtotal gastrectomy among 2. The other 4 patients were in inoperable advanced stage. In their treatment, 4 patients who were stage III at the diagnosis underwent the Macdonald's protocol: 5-fluorouracil 425 mg/m^2/day (days 1 to 5) plus folinic acid 20 mg/m^2/day (days 1 to 5), one month later: 5-FU 400 mg/m^2/day (days 1 to 4) plus folinic acid 20 mg/m^2/day (days 1 to 4) and the last 3 days – radiotherapy (RT) 1.8 Gy/day to 45 Gy; one month after completion of RT: 5-FU 425 mg/m^2/day (days 1 to 5) and folinic acid 20 mg/m^2/day every 4 weeks × 2 cycles (scheme FUFA). Another 4 patients (with metastasis detected after adjuvant therapy, and 2 of the 4 patients with synchronous metastasis) received first-line palliative chemotherapy. This group underwent Van Cutsem's protocol: docetaxel 75 mg/m^2/day and cisplatin 75 mg/m^2/day, plus 5-FU 750 mg/m^2/day (days 1 to 5) every 3 weeks (scheme DCF). Uyeturk *et al.* [2013] noted that postoperative chemoradiotherapy reduced the risk of local recurrence in locally advanced gastric cancer. Moreover, postoperative chemoradiotherapy had the benefit of progression-free survival and overall survival. Thus, palliative radiotherapy may be considered as a treatment option for unresectable or metastatic gastric carcinoma. In addition, chemotherapy combined with the best supportive care (BSC) can improve the OS of these patients. Uyeturk *et al.* [2013] also demonstrated the superiority of combination chemotherapy over monotherapy regimens for symptom control and response rate. A significant improvement in PFS, OS and response rate has thus been demonstrated among gastric cancer patients who undergo the DCF scheme [12]

In the quoted studies, in patients with gastric originating Krukenberg tumor, an overall survival advantage has been demonstrated in favor of cytoreductive surgery in combination with HIPEC, in relation to surgery alone. This benefit has, however, not been observed in the absence of peritoneal disease.

In other work, the median overall survival was 40 months among 75 patients with ovarian metastases from colorectal origin who received cytoreductive surgery in combination with HIPEC. Of these patients, 19% had a diagnosed Klukenberg tumor without peritoneal disease, and among these patients, a significantly higher three-year OS was observed, compared to those with peritoneal disease (77% vs. 48%).

At present, there is insufficient evidence for the routine use of HIPEC in Krukenberg tumor, especially in cases of minimal disease or without evidence of peritoneal disease. It should thus be noted that the potential oncological benefit should always outweigh the possibility of the additional side effects associated with cytoreductive surgery in combination with HIPEC [4].

CONCLUSION

Systemic chemotherapy is an independent predictor of good prognosis. Still, the survival rate of patients with Krukenburg tumor who have received chemotherapy has significantly improved. Surgical treatment should, therefore, be considered for patients with Krukenberg tumor even if metastases are present outside the ovaries. Higher survival rate has also been observed among patients who have undergone complete cytoreduction in combination with chemotherapy, providing there were no evidence of metastases beyond the pelvis. Of such chemotherapy, platinum-based chemotherapy received in gastric tumors and 5-FU+ LV, in combination with oxaliplatin in colorectal cancer appear to improve prognosis and outcome. This disease includes heterogeneous group of tumors with different types, thus further randomized studies are needed to increase the effectiveness of the treatment. It must be underlined that accurate diagnostic evaluation prior to surgery has important implications for proper treatment.

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