Target treatment of Slovenian patients with metastatic gastrointestinal stromal tumours

Mojca Unk, Erika Matos, Darja Eržen, Branko Zakotnik

In the last 30 years, major progress has been made in the classification, diagnosis and treatment of gastrointestinal stromal and mesenchymal neoplasms. Gastrointestinal stromal tumours (GIST) represent less than 1% of all malignant gastrointestinal tumours. The clinical picture depends on the site, size and malignant potential of the GIST. Metastatic GIST is a case of successful treatment, as the detection of KIT- and PDGFR-signalling pathways and kinase inhibitors, such as imatinib, mesylate and sunitinib, has significantly improved the prognosis of this disease. The treatment outcome in Slovenian patients with metastatic GIST is comparable to the treatment outcome observed in patients treated in major international clinical trials. We used the follow-up protocol which, besides contrast computed tomography of the abdomen, also included ultrasound of the abdomen. By doing so, along with comparable survival rates, we improved the quality of life of our patients and reduced the treatment costs.

Surgical treatment of breast cancer in patients aged 80 years or older – how much is enough?

Nikola Bešić, Hana Bešič, Barbara Perič, Gašper Pilko, Rok Petrič, Jan Žmuc, Andraž Perhavec

The population of older people is increasing and so is the population of breast cancer patients aged 80 years or older. Unfortunately there is no consensus or recommendations on how to treat older breast cancer patients. The aim of our retrospective study was to identify the most appropriate surgical treatment of breast cancer in patients aged 80 years or older and to determine their survival. We reviewed the medical records of 154 patients with early-stage breast cancer (mean age of 83 years; ranging from 80 to 90 years), who underwent surgery at the Institute of Oncology Ljubljana in the period from 2000 to 2008 when they were aged 80 years or older. We collected data on the extent of the disease, pathomorphology of the tumour, treatment method, extent of breast and axillary lymph node surgery, disease recurrence, cause of death, length of survival, and length of survival for breast cancer. Using univariate and multivariate analyses, we also determined the correlation between prognostic factors, type of treatment and survival. Breast cancer was growth in the breast in 28%, whereas 47% of patients were diagnosed with regional metastases, and the extent of the disease was unknown in 25%. 75% of patients were staged as pT1/pT2, while 25% had stage pT3/pT4 tumours. Surgical treatment comprised: quadrantectomy (in 27%), mastectomy (in 73%), axillary dissection (in 57%), sentinel lymph node biopsy (in 18%), and 25% of patients had no axillary surgery. A total of 88% of patients received adjuvant hormonal treatment (tamoxifen - 53 patients, aromatase inhibitor - 45 patients, a combination of both - 37 patients), while 1.3% of patients were treated with cytostatics, and 16% underwent biopsy. During follow-up of 0.1 to 11 years (median 4.45 years), disease recurrence was observed in 23%. Local recurrence of the disease was observed in 10%, regional recurrence in 6% and distant metastases in 23%. Five-year survival for breast cancer was 90% in locally limited cancer and 62% in regionally advanced cancer. One of the patients died on the first day after surgery due to a myocardial infarction. A total of 19% of all patients died of breast cancer, and 12% died of other causes. The univariate analysis showed that the length of survival of breast cancer patients was correlated with the following factors: treatment with hormones before surgery, pathological T-stage, pathological N-stage, breast surgery, lymph node surgery, oestrogen receptors, degree of tumour differentiation, radicality of surgery, and surgical treatment according to the established guidelines. Using the multivariate statistical analysis, we found that the pathological T-stage, pathological N-stage and oestrogen receptors were independent prognostic factors for the duration of survival of breast cancer patients. The results of our multivariate analysis show that surgeons adjusted the extent of operative treatment according to the stage of the disease and the general condition of the patient. Short survival for breast cancer indicates that, in patients aged 80 years or older, breast cancer with metastases in axillary lymph nodes can be a very aggressive disease.

Treatment of the consequences of irradiation of pelvis minor with hyperbaric oxygen

Barbara Šegedin, Ana Perpar, Primož Petrič

Radiation therapy is an important part of treatment of tumours of the pelvis minor. Late effects can develop months or years after treatment, and they occur in a severe form (RTOG grades 3 or 4) in 5-15% of irradiated patients. In the last few years, besides other invasive and non-invasive methods, radiotherapy-induced late complications have also been treated with hyperbaric oxygen therapy. Such treatment first proved successful in the treatment of osteonecrosis of the jaw, while in the last few years, the studies have confirmed that hyperbaric oxygen therapy is also effective in the treatment of post-radiation cystitis and proctitis. Hyperbaric oxygen therapy minimises the likelihood of complications, reduces the already developed symptoms and signs, and significantly improves the quality of life. In the last six years, only seven patients were treated with hyperbaric oxygen therapy at the Institute of Oncology Ljubljana for post-radiation injuries developed due to pelvic irradiation, although such treatment should be provided to 40-50 patients annually.

Multiple faces of the Lynch syndrome: detection of germ-line mutations in the MSH6 gene

Uršula Prosenc Zmrzljak, Srdjan Novaković

The Department of Molecular Diagnostics at the Institute of Oncology Ljubljana has introduced testing of germ-line mutations in the MSH6 gene. Mutations in this gene are associated with the Lynch syndrome and represent an increased likelihood for the development of colorectal, endometrial, ovarian, and other cancers. The presence of mutations in the MSH6 gene is tested using the direct sequencing method and the MLPA multiplex ligation-dependent probe amplification) method. While sequencing allows us to detect point mutations and small deletions and insertions, the MLPA method is used to detect the presence of large deletions and insertions in the gene or a deletion of the entire gene. Mutations in the MSH6 gene are tested in persons who, in the process of genetic counselling, show an increased likelihood of developing Lynch syndrome. A timely detection of mutations in the genes associated with the development of cancer is important for the carriers of mutations, as a proven mutation is a reason for individualised clinical monitoring and/or preventive measures in mutation carriers.

14th World Congress on Gastrointestinal Cancer

Irena Oblak, Stojan Potrč

The 15th World Congress on Gastrointestinal Cancer took place from 3 to 6 July 2013 in Barcelona. This is a global event addressing individual types of gastrointestinal cancer in accordance with the latest recommendations and findings, from diagnosis to treatment. The focus is on individual management of each patient and the importance of a multidisciplinary approach, including the most recently discovered molecular mechanisms. Over 60 world-renowned lecturers, all experts in their fields, presented the latest findings and recommendations or lead small targeted groups of physicians who attended sessions on specific topics. At the Congress, the participants were also given the opportunity to present their research results, with their abstracts being published in the Annals of Oncology. Two Slovenian abstracts were presented, both from the field of post-surgical treatment of gastric cancer. In the following pages, we will present only some of the new findings and the outlines presented at the Congress.

Biopsy of resectable liver metastases of colorectal cancer: an article with several shortcomings

Živa Pohar Marinšek

This year's last issue of the journal Onkologija included an article entitled “Biopsy of resectable liver metastases of colorectal cancer – an unnecessary and dangerous method”. In this article, the authors warn against the use of fine-needle biopsy (FNB) of liver metastases of colorectal cancer (CC), as this procedure could threaten the survival of patients. In this article, we want to highlight the shortcomings of the previously mentioned article and warn against the sensational title of the poorly written article which imposes its message on the readers without any clear justification.

Guidelines for the management of patients with squamous cell carcinoma of the anal canal and perianal skin (anal margin)

I. Oblak, V. Velenik, F. Anderluh, M. Skoblar Vidmar, J. But Hadžić, E. Brecelj, M. Reberšek, F. Jelenc, S. Potrč

Cancer of the anal canal and anal margin is a rare disease. In Slovenia, on average 20 patients are diagnosed with this disease each year, more women than men. However, the incidence has increased in the last year, mainly in young, homosexual men, most probably due to infections with the sexually-transmitted human papillomavirus (HPV) and human immunodeficiency virus (HIV), which are known causal agents of this disease. Cancer of the anal canal and anal margin is primarily a locoregional disease, as distant metastases are found in less than 10% of the patients. Radical radiochemotherapy plays the central role in the treatment of anal canal and anal margin carcinomas with no distant metastases, except in well-differentiated anal margin carcinomas smaller than 2 cm, where local excision is advised. Radical radiochemotherapy provides a complete response in as many as 80-90%, which is reflected also in an excellent treatment outcome with 5-year survival of 80%. Patients clinically staged as cT1-2 stand a 6.5% chance of developing inguinal lymph node metastases, while the likelihood in patients staged as cT3-4 is 16%. Surgery, namely abdominoperineal excision, has a role in the treatment of residual disease after radical radiochemotherapy.
In the future, HPV vaccines hold great promise for the prevention of this virus-induced disease.

Palliative sedation

Jožica Červek

Palliative sedation is the controlled use of medications intended to induce and maintain the state of reduced consciousness. In this state, the patient does not suffer from symptoms that we can no longer control (refractory symptoms). The most frequent reasons for palliative sedation are uncontrollable terminal anxiety and difficulty breathing.

Midazolam is the medicine of choice for palliative sedation. The appropriate dose is determined by gradually increasing the initial dose until the desired effect – symptom control (titration) – is reached. The palliative sedation protocol sets out a clearly defined medical indication, the management and instructions for medical care as well as legal and ethical principles. Palliative sedation is not a synonym for euthanasia, nor does it shorten life.

Surgical treatment of colon cancer

Mirko Omejc

The extent of resection for colon cancer depends on the tumour site and vascular anatomy. Lymphatic drainage is applied along the veins in one, two or three directions, where cancer might metastasise. In surgery, it is necessary to maintain a safety margin proximally and distally to the tumour and to remove the potentially affected locoregional lymph nodes. The aim of surgical treatment is radical resection (R0), which is the only potentially curative treatment for this disease.

Referral and management of patients with melanomas and epitheliomas

Tanja Planinšek Ručigaj

The population has become increasingly aware of the importance of health care and knows the risk factors for individual diseases, e.g. the harmful effects of sun rays and their influence on the development of skin cancer, which represents a major problem for a relatively large number of dermato-venereologists dealing with an increasing number of patients. Besides regular examinations, many other patients with an urgent or immediate referral visit the dermato-venereology clinics on a daily basis due to long waiting times, but this only prolongs them.

Imaging in patients with malignant melanoma

Maja Mušič

Imaging is performed in patients with malignant melanoma (MM):

1. To stage the disease
2. During follow-up
3. In disease recurrence

Surgical treatment of melanoma

Marko Hočevar

From the treatment perspective, skin melanoma is a surgical disease, as surgery is a very important treatment modality for all stages of this disease. We distinguish between surgical treatments of primary lesions and regional, in-transit and distant metastases. Considering the primary lesion, we distinguish between diagnostic and wide (radical) excision, with the safety margin being up to 5 mm and 1-2 mm, respectively. Depending on their size, locoregional melanoma metastases are either clinically occult or clinically apparent. The first are detected with the help of sentinel lymph node biopsy and are afterwards treated in the same manner as clinically apparent metastases, namely with radical lymphadenectomy of the regional lymph node basin. In-transit metastases can be treated with a simple excision or, in cases of multiple metastases located on the extremities, with the help of technically demanding isolated limb perfusion or infusion. In a systematic assessment, surgical treatment is always the first choice if metastases can be removed completely.

Lymphoedema in melanoma patients

Tanja Planinšek Ručigaj

Secondary lymphoedema is one of the most common complications after the surgical treatment of malignancies. The incidence rate depends on the cancer site and therapeutic measures. It occurs in one third of all cancers, either due to the disease itself or because of the growth of metastases interfering with the lymphatic fluid drainage, due to lymphadenectomy or surgical removal of the primary tumour, where the surgical procedure can damage the lymphatic pathways, or as a result of fibrous changes to the tissue after radiotherapy, which also interferes with lymphatic fluid drainage. The incidence of lymphoedema is common in the treatment of melanoma, yet still unrecognised in Slovenia. If left untreated, lymphoedema often leads to recurrences of erysipelas and an enormous enlargement of a specific body part. Therefore, prevention and early detection of lymphoedema with referral for appropriate treatment are of utmost importance. To prevent late diagnosis and treatment of lymphoedema after cancer treatment and subsequent complications, the physician must actively look for signs and symptoms of lymphoedema during patient follow-up and immediately treat such patients or refer them for further treatment. To continue, it is even more important that the patient gets the information about the possibility of developing lymphoedema already during treatment of the primary disease, and that the patient detects the swelling early enough and reports it to his/her therapist who must then refer the patient for immediate lymphoedema treatment. The treatment consists of a decongestion phase, where the oedema is evacuated using different methods, most often compression therapy with short-stretch bandages, and a maintenance phase, where we maintain the non-oedematous state using medical compression aids.

Melanoma: treatment with radiation therapy

Primož Strojan

Surgery is the therapy of choice for melanoma. However, as it is non-radical, or if the histopathological examination shows presence of adverse predictive indicators, additional (adjuvant) treatment is necessary. Radiation therapy, either curative or palliative, proved to be effective. Moreover, if we follow the modern principles of the discipline and use advanced technology, it is also safe. Therefore, radiation therapy is today an indispensable part of the multidisciplinary management of melanoma patients.

Systemic treatment of melanoma

Janja Ocvirk

Melanoma is a curable disease if detected early, but in its advanced stages, it remains incurable. Surgery is still the primary treatment for local, regional and isolated metastatic disease. The risk for disease recurrence is 50% in patients with melanoma thicker than 4 mm and 50-85% in patients with lymph node involvement, depending on the number of the involved lymph nodes. To reduce the number of disease recurrences in high-risk melanoma patients, they are treated adjuvantly with interferon-α (IFN-α). The IFN-α is effective if used in high doses. Patients undergoing such treatment are less likely to experience disease recurrence and their 5-year overall survival rate has improved by 24%. Treatment also has adverse effects that are controllable. Other medicines used in adjuvant treatment are not effective enough to significantly impact patients' survival. Metastatic melanoma is an incurable disease and patient survival is short despite treatment. Different schemes, in combination with either cytostatics alone or cytostatics with immunotherapy, induced more responses to treatment than monotherapy with cytostatics. However, they failed to prolong the survival of these patients, and resulted in a higher incidence of adverse effects. Monotherapy with the cytostatic dacarbazine thus remains the standard chemotherapy for treatment of patients with metastatic melanoma. In the last few years, clinical trials tested several new target drugs and immunotherapy. Ipilimumab and vemurafenib showed clinical effectiveness in terms of prolonging the time to disease progression and overall survival. Moreover, there are also several ongoing studies examining the effectiveness of different target drugs, antibodies and various combinations thereof.

Electrochemotherapy of melanoma

Gregor Serša, Maja Čemažar, Nebojša Glumac, Marko Snoj

Electrochemotherapy is an anti-cancer treatment that combines the use of standard chemotherapeutics and application of electric pulses at the tumour site. This increases the effectiveness of bleomycin or cisplatin but only in the area of the delivered electric pulses. In Europe, electrochemotherapy is currently the established method for treating different skin tumours, and it is particularly effective in the treatment of skin and subcutaneous melanoma metastases. Its effectiveness is around 80% in terms of objective responses and around 60% in terms of complete responses after a single therapy, with the possibility of improving the response with ongoing therapy. Electrochemotherapy is used primarily in the treatment of skin, subcutaneous and transit melanoma metastases and bleeding tumours and metastases at previously treated sites.

Stereotactic surgery of malignant melanoma brain metastases

Uroš Smrdel

Since 2007, the Oncology Institute of Ljubljana carried out 97 SRS procedures, 9 of which were performed in patients with malignant melanoma brain metastases. Another patient was treated with hyperfractionated stereotactic radiotherapy (hfSRT), as the irradiated area was too large for irradiation with SRS and, based on the radiobiological characteristics of the tumour, we decided for targeted radiation therapy with a higher daily dose (6). Median survival was 30 weeks for all malignant melanoma patients, with the same survival time until local recurrence of the disease. Following SRS, there were less local recurrences among patients compared to progressions or recurrences of the disease outside the central nervous system (CNS). The irradiation dose delivered to patients treated with SRS was 22.5 Gy (20-25) in a single dose. The patient treated with hfSRT received 30 Gy in total, namely 5 doses of 6 Gy. Eight out of nine patients also received WBRT, and one was treated with WBRT after the first surgery for brain metastases and did not receive it after the SRS. The patient treated with hfSRT due to systemic therapy administered after radiation therapy (vemurafenib) did not receive WBRT and experienced disease progression in the CNS outside the irradiated three months later. The response was achieved in all patients (a stable disease in 4 patients, a partial response in 4 patients, a complete response in 1 patient), with patients with a stable disease experiencing disease progression outside the CNS a few weeks after the therapy. A complete response was achieved in one patient, but six months later, he also experienced disease progression in the CNS outside the SRS area.

Treatment of metastatic malignant melanoma with vemurafenib - case report

Marko Boc, Nina Boc, Tanja Mesti, Martina Reberšek

In Slovenia, just like everywhere else in the world, we are witnessing an upward trend in the incidence of malignant melanoma of the skin. According to the data from the 2009 Cancer Registry of Slovenia, Slovenia recorded 298 and 415 new cases of malignant melanoma in the years 2000-2004 and 2005-2009, respectively. It is estimated that in 2012, there were 555 new cases of malignant melanoma. This melanoma is more common in women than in men, and it represents the sixth most common malignancy in women and the eight most common malignancy in men (1).

A multidisciplinary approach in the treatment of malignant melanoma is necessary to ensure the best possible outcome for the patient. Collaboration between the dermatologist, surgeon, pathologist, medical oncologist and radiotherapy specialist is important and necessary. The most important are prevention and early detection, because it is crucial to detect the disease soon early, when it is still curable. The higher the stage of the disease at detection, the greater the likelihood of distant metastases when the disease becomes incurable. This happens in more than 50% of patients with stage 3 malignant melanoma. Median survival for metastatic disease is short (6-9 months), and until the use of newer medicines, it rarely exceeded 12 months (2).

However, new hope for patients comes with new targeted therapies, such as vemurafenib and ipilimumab, which, according to the currently available data, provide better response rates and prolong the survival of patients with metastatic malignant melanoma as opposed to cytostatic drugs (3, 4).

In our clinical case, we present a patient with metastatic malignant melanoma who has been treated with a number of lines and types of systemic therapy, including vemurafenib, a selective inhibitor of the oncogenic BRAFV600E mutant kinase.

Imunomodulators in the treatment of malignant melanoma - case report

Tanja Mesti, Marko Boc, Martina Reberšek

The incidence of melanoma is increasing, both in Slovenia and world-wide, more than any other form of cancer. According to the Cancer Registry of Slovenia, 415 patients were diagnosed with this disease in 2009 (1). Surgical removal of skin melanoma is the primary curative treatment for patients with early-stage disease. There are approximately 80% of such patients. In high-risk patients (around 10%), we also recommend treatment with high doses of interferon-α2b (2, 3). Metastatic melanoma is still an incurable disease with a 5-year survival of less than 5%. However, the prognosis for these patients has improved in the last few years, thanks to new developments in the field of systemic treatment. Besides standard treatment with systemic chemotherapy, new registered medicines are now also available with a different mechanism of action than chemotherapy, such as immunotherapy with the monoclonal antibody ipilimumab, BRAF inhibitors vemurafenib and dabrafenib, and MEK inhibitors (2, 3).

Suicide as a late consequence of cancer treatment in childhood. All three cases in Slovenia

Borut Škodlar, Berta Jereb

Patients treated for childhood cancer are particularly vulnerable to suicide. There is increased suicidal ideation and a high incidence of suicide among them. In Slovenia, we have recorded no increase in the suicide rate in this group of patients. Out of 1,647 patients who were treated for cancer in childhood, only three died by suicide. The following article presents all three patients who committed suicide. With the help of the available data, we established the similarities and differences that contributed to the development of suicidal behaviour in each of these three patients. We can find that despite the differences in the course and treatment of the disease, all three patients had one thing in common: none of them received professional psychological help intended for patients after childhood cancer treatment. The development of a well-functioning professional network in this field would enable the inclusion of a larger number of patients, allowing them to speak out about their psychological problems. By doing so, we would contribute significantly to preventing suicide in this vulnerable group of patients.

Case report of a patient with a metastasis in the L1 vertebral body of unknown origin

Marko Hanc, Janez Ravnik, Igor Movrin, Rajko Kavalar, Gregor Rečnik

Metastases of bone malignancies are much more common than primary neoplasms. The site of origin remains unknown in approximately 2% of metastases. We present a case of a 59-year-old patient referred to our Institute for pathological fracture of the L1 vertebral body. After removing the majority of the body, a detailed pathological examination and extensive diagnosis, the question of primary tumour origin still remains unsolved.