SESSION 2

EMERGENCIES IN ONCOLOGY
Intracavitary brachytherapy as the intensive therapy of severe metrorrhagia caused by advanced gynecological neoplasms

Key words: Intracavitary brachytherapy; Gynecologic cancer; Metrorrhagia

Frequently, one of the manifestations of the advanced invasive carcinoma of the cervix, endometrium or recurrent carcinoma is metrorrhagia. If chronic bleeding occurs, the patient may complain of fatigue or other symptoms related to anemia. But sometimes the bleeding can be so severe as to be life-threatening (1). In this case bleeding can be temporized by vaginal packing which can be repeated few times. If the vaginal packing does not give satisfactory haemostasis the surgical treatment is taken into consideration. These treatments need more intensive medical care, with antibiotics and transfusional therapy (2). Transfusion, and advanced carcinoma associated with pelvic infection and tumor necrosis can result in complications such as acute intravascular haemolysis, disseminated intravascular coagulation (DIC), acute renal failure, and aggravated patients general condition (3).

Ionizing radiation affects the malignant tumors by the injury such as cell death but also with the radiation injury of the tumor blood vessels (neovascularisation) and the blood vessels of surrounding tissues. Histologic examination after the exposure of blood vessels to radiation, shows edema and swelling of endothelial cells, followed by narrowing of lumen. Later a thrombus may be formed and occlude lumen completely as the final effect (4).

Radiation therapy is the most important modality of oncology treatment in advanced gynecological neoplasms. External pelvic irradiation is usually delivered prior to intracavitary insertion within one week, to reduce the tumor masses, bleeding, and infection, as the dose of 10Gy is enough to produce thrombosis and occlude the blood vessels. Further treatment plan considers the brachytherapy which allows irradiation with a high dose to be delivered directly to the tumor, cervix and endometrium. Transvaginal irradiation is used before the start of external radiotherapy for large lesion and in the case of severe metrorrhagia to produce hemostasis. Intracavitary radioisotope insertion using applicators consisting of intrauterine tandem and vaginal colpostats or cylinders, in remote after-loading technique (5).

Brachytherapy produces hemostasis by the radiation effect on the blood vessels. The rapid necrosis of the tumor cells occurs, as a result of irradiation, with delivered several cytokines, which are involved in coagulation, and can intensify hemostasis. High dose of irradiation in brachytherapy produces irradiation effect within few minutes to 24 hour, with fast produced hemostasis. The treatment can be repeated after some time, if hemostasis is not satisfactory (4).

A small number of teletherapy and brachytherapy units in our country and numerous patients with neoplasms create some problems, especially in oncology emergencies like metrorrhagia. In our country we are talking about hemostasis intracavitary application if the brachytherapy insertion is used in therapy of severe metrorrhagia. This medical term is not common in terminology abroad as the complete effects of therapy are considered when radiotherapy is in question.

In the period of two years, 44 patients were treated at our Institute with irradiation treatment with hemostatic endocavitary brachytherapy because of metrorrhagia - either in frame of radical irradiation treatment or palliative treatment.

The majority of patients (39) had carcinoma of the cervix and 5 had endometrial carcinoma. Three patients were treated due to the local relapses. Histological form corresponded to the localization (site) of malignomas, with the most frequent carcinoma of the cervix advanced form - stage IIIb (51,3%), exophytic forms (86,36%). It is well known that carcinoma of the cervix in this form, on histological level, shows newly formed blood vessels which are large, of sinusoid character that explains metrorrhagia (1, 8, 9). At the same time this explains good effect of irradiation for hemostasis as well as the total good response to radiotherapy.

Hemostatic effect could be reached mainly with only one application (93,2%), revealing that the majority of patients had only one vaginal packing during 24 h (34,1%) or had no vaginal packing (31.8%). In a small number of patients, vaginal packings had to be repeated up to 4 times at maximum (7).

The failure of hemostatic application can be explained by the lesion mass followed by the tumor necrosis and widely opened blood vessels. Conditions with impaired coagulation and clinically undetected DIC also can be the cause of hemostatic application failure (3). Unfortunately, due to the intervention that is urgent, frequently all parameters for blood analysis are not available.

Good hemostatic effect and application performed immediately after the start of metrorrhagia made blood transfusion unnecessary in the majority of cases (24 pts). Decreased associated infection, tumor mass and improved general condition of patients lead to faster recovery of suppressed bone marrow (1, 5).

The most frequently applied doses were TD 9Gy, TD 10Gy or TD 7Gy to the site of tumor lesion itself, calculated according to the tumor size in relation to the surrounding anatomic structures and type of applicator was conditioned by the site of the underlying lesion (uterine - intrauterine probe, ovoides, vaginal applicator) (7). Total treatment dose involves the dosages delivered in hemostatic purposes, unless the dose was not delivered exclusively into the tumor (1, 5).

If the palliative radiotherapy is in question (carcinoma of the cervix stage IV, relapses) and oncologically incurable patients, such a therapy conducted in a satisfactory number of applications can provide more comfortable life and less medicamentous therapy (1, 5).

Intracavitary brachytherapy, in our conditions, especially for out-patient treatment, in order to achieve hemostasis is justified, regarding that this is an intervention easy to be performed. It also has economic advantages and in addition to the improved patients comfort during radi-
cal or palliative treatment, it can be considered as quite suitable and ade-
quate intensive therapy of severe metrorrhagia caused by advanced gynec-
ologic neoplasms.

REFERENCES

9. Čeraniæ J. Otkrivanje i razlučivanje adneksalnih tvorbi s pomoću transvaginalnog obo-
caused by a malignant disease at the Institute for Oncology and Radiology of Serbia. We treated 12 women and 33 men, their median age being 55.86 years (range 27 to 73). The predominant symptoms were: facial oedema, choking, dyspnea, cough, hemoptysis, neck vein distension, and rarely, hoarseness and swallowing difficulties. The most frequent cause of the SVCS is bronchogenic lung cancer- 84%, or 38 of 45 patients. The data in the Table 1 show that SCLC is the most frequent cause of the SVCS.

Table 1. Pathohistological (PH) forms of the malignancies that cause SVCS

<table>
<thead>
<tr>
<th>PH</th>
<th>Number of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell lung cancer</td>
<td>21</td>
<td>46.66</td>
</tr>
<tr>
<td>Planocellular lung cancer</td>
<td>14</td>
<td>31.11</td>
</tr>
<tr>
<td>Adenocarcinoma of the lung</td>
<td>2</td>
<td>4.44</td>
</tr>
<tr>
<td>Unknown histological type</td>
<td>2</td>
<td>4.44</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>1</td>
<td>2.22</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>1</td>
<td>2.22</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2</td>
<td>4.44</td>
</tr>
<tr>
<td>Anaplastic thyroid cancer</td>
<td>1</td>
<td>2.22</td>
</tr>
<tr>
<td>Pleural mesothelioma</td>
<td>1</td>
<td>2.22</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>100</td>
</tr>
</tbody>
</table>

At the beginning of the treatment, the disease was localized in all the patients who had bronchogenic lung cancer with the SVCS. Twenty of 21 patients with the SCLC began the treatment with chemotherapy. In most of the cases, four cycles (range 1 to 6) were applied, and one patient was treated with radiotherapy only. The total of 11 patients had a partial response to the applied chemotherapy. After the initial partial response 6 of those 11 patients developed SVCS before the onset of radiotherapy. One patient responded completely, and the response was estimated as a stable disease in 7 patients. The progression of the disease was observed in one patient.

Of 14 patients with poorly differentiated planocellular lung cancer, 7 began their treatment with chemotherapy, and radiotherapy was applied only in 7 patients. Two patients with adenocarcinoma of the lung also began their treatment with chemotherapy, but there was no response to the treatment in these patients. Other patients with various PH forms began their treatment according to the protocols, with palliative radiotherapy being delivered when SVCS develops, after the primary treatment.

Table 2. Treatment of the SVCS in patients with lung cancer

<table>
<thead>
<tr>
<th>PH</th>
<th>HT</th>
<th>RT after HT</th>
<th>RT only</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell lung cancer</td>
<td>20</td>
<td>20</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Planocellular lung cancer</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>27</td>
<td>16</td>
<td>82</td>
</tr>
</tbody>
</table>

Karnofsky performance status was estimated in all the patients before the initiation of the radiotherapy, and it ranged from 70 to 100%, with 2 patients having KI less then 70%, 8 patients with KI 70%, 20 with KI 80%, and 5 with KI more than 80%. That influenced the choice of the radiotherapy regimen.

Table 3. Radiotherapy regimen

<table>
<thead>
<tr>
<th>PH</th>
<th>20/8</th>
<th>30/10</th>
<th>45/22</th>
<th>8/1</th>
<th>60/28</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell lung cancer</td>
<td>6</td>
<td>5</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Planocellular lung cancer</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Adenocarcinoma of the lung</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Unknown histological type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Anaplastic thyroid cancer</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pleural mesothelioma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>12</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

Response to the delivered radiotherapy: in 7 patients (15.5%), of the total of 45 treated with radiotherapy, the response was estimated as a complete regression of the syndrome. In 21 patients (46.6%) the response was estimated as a partial remission. The response was valued as stable in 31.11%, and 3 patients (6.66%) suffered from the progression of the syndrome.

Table 4. Survival time after the application of radiotherapy

<table>
<thead>
<tr>
<th>Survival time (months)</th>
<th>Number of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>12</td>
<td>26.66</td>
</tr>
<tr>
<td>3-6</td>
<td>14</td>
<td>31.11</td>
</tr>
<tr>
<td>6-9</td>
<td>10</td>
<td>22.22</td>
</tr>
<tr>
<td>9-12</td>
<td>4</td>
<td>8.88</td>
</tr>
<tr>
<td>&gt;12</td>
<td>5</td>
<td>11.11</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>100</td>
</tr>
</tbody>
</table>

The mean survival time is 9.48 months, range being 1 to 48 months.

CONCLUSION

Clinical symptoms of the SVCS require urgent treatment. Our results indicate a quick withdrawal of the syndrome after radiotherapy in 62.22% of cases, some reports indicating the efficacy of radiotherapy in over 70% of the cases.

SCLC, as the commonest cause of the syndrome, requires the use of a combined treatment, both chemotherapy and radiation. The effect of the radiotherapy in treating SVCS caused by malignant diseases greatly depends on the HP form of the malignancy, as well as the stage of the disease.

REFERENCES

Compressive syndromes caused by secondary tumours of central nervous system

Key words: CNS metastases; Intracranial pressure; Radiotherapy

Even though metastases to organs other than the brain are more common, brain metastases are more debilitating and more rapidly fatal if untreated than metastases to other organ systems. 25% (or 131000) of the 527000 cancer patients expected to die each year in the USA ultimately develop intracranial metastases. Brain metastases from solid tumours are solitary in about 50% to 65% of the cases when the diagnosis is made during life. In 9% of patients the brain metastases may be the only apparent site of cancer. Statistics indicate that patients treated by operation and irradiation survive longer with a higher quality of life than those who undergo radiotherapy alone do. Breast cancer, after lung cancer is the second most common source of metastases to the CNS. In contrast to most other cancers, breast cancers tend to more commonly involve all intracranial and intraspinal compartments: bone, meninges, parenchyma, and can involve two or more compartments simultaneously. The goal of surgical intervention is to decompress brain and spinal cord to preserve neurologic function and provide the time necessary for chemotherapy and radiation therapy to exert their efficacy (1,2).

Metastatic tumors in general and from the breast in particular, reach the CNS primary by the intravascular route. Blood-borne metastases can reach and grow in any tissue supplied by blood vessels: bone, meninges, parenchyma, and can involve two or more compartments simultaneously. The surgical intervention is to decompress brain and spinal cord to preserve neurologic function and provide the time necessary for chemotherapy and radiation therapy to exert their efficacy (1,2).

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treated. Whole-brain irradiation is more controversial. This practice is based on the assumption that other microscopic metastatic tumors not yet visualized on CT and MR, may exist throughout the brain. However the efficacy of whole brain irradiation following the successful removal of a brain metastasis has not yet been proved by prospective clinical trials and whole-brain radiation therapy has been found to be associated with dementia. With the wide spread availability of high resolution MRI that is very sensitive for metastatic disease, this practice is now being called into question and national study is investigating the role of postoperative radiation therapy in CNS metastatic cancer (9).

Stereotactic radiosurgery is based on many beams of radiation intersecting at a precise point. At that point the radiation dose is additive so that the radiation delivered to the point is very high. Typically stereotactic radiosurgery is done in a single treatment session. There are two general methods of delivering stereotactic radiosurgery: gamma knife and stereotactic linear accelerator. With the gamma knife radiation from 201 cobalt sources arranged in a spherical pattern are collimated into narrow beams directed to the center of the sphere. In stereotactic linear accelerator radiotherapy a radiation generator tube is rotated about a patient’s head directed the constant beam toward a present center (isocenter) point (10).

A malignant tumor that metastasizes to the spine has the potential for adversely affecting the patients quality of life in a most profound fashion. It is also possible that prevention of paraplegia and a sphincter deficit will result not only in an improved quality of survival but longer survival as well. Pain is the most common presenting symptoms of spinal metastases. Even in patients whose first symptom is neurologic deficit, careful questioning will reveal that pain preceded the onset of neurologic symptoms by days or weeks loss of diminution of pinprick or light touch perception in the trunk may provide a general idea of the level of spinal cord compression in the thoracic spine.

Motor deficit may result from compression of the spinal cord of the nerve roots of the cauda equina. Compression of the upper motor neurons contained within the spinal cord may produce increased deep tendon reflexes.

Radiotherapy is the mainstay of treatment producing symptomatic improvement in three of four patients with metastases to the CNS. The RTOG was not able to demonstrate a difference in survival with doses ranging from 2000 cGy in five treatments over 1 week to 4000 cGy in 20 treatments over 4 weeks. Survival ranged from 3.7 to 4.5 months from treatment. For the patients with little or no other metastatic disease a longer course of treatment is justified to minimize neurotoxicity which may be related to the larger dose per treatment used with shorter courses of therapy.

Radiotherapy of carcinomatous meningitis produces symptomatic improvement in two of three patients. For those who did respond median survival is about 6 months. Since treatment is palliative some recommend that radiation be directed only that the lesion producing symptoms. Thus if cranial nerves are affected only the skull base is treated. Localized deposits along a spine may also be treated. It is vital to image the entire spine with contrast enhanced CT or MRI to assure that the full extent of disease is treated.

Choroidal metastases are the most common intraocular neoplasms. However, the incidence of clinically symptomatic intraocular secondary tumors is lower. The veal tract is the most common site of intraocular metastasis probably due to anatomical reasons and blood vessel supply. According to autopic studies the incidence of microscopic asymptomatic choroidal metastasis in patients with disseminated cancer is between 4 and 12% (11,12). At the time of diagnosis about 20-40% of patients had macroscopic bilateral choroidal metastasis. Radiotherapy is an efficient and safe palliative treatment for choroidal metastases and it helps the preservation of vision. Thus there is a major impact on the quality of life in a group of patients with the almost uniformly fatal prognosis.

Radiotherapy is an effective palliation for bone pain with overall response rates consistently greater than 80% and is the treatment of choice for most patients with neurological complications from a bone metastasis. Radiotherapy will enable pain relief and healing after pathological fracture in most patients with bone metastases irrespectively to pathohistology. It may also have a role in prevention of neurological complications and pathological fractures by prophylactic treatment of a symptomatic metastases (13).

Since the early 1980’s the optimal radiotherapy treatment schedule for palliation of pain full bone metastases has been under debate. Several non-randomized and randomized studies indicated that one fraction or a few fractions could be as effective both in the incidence of pain relief and in the duration of response as the normally used multiple fractionated schedules (14,15).

REFERENCES

Malignant tumors and obstructive uropathy

Key words: Obstructive uropathy; Treatment; Prognosis

Almost one fourth of those having malignant disease localized on organs of the small pelvis and retroperitoneum develop acute obstructive uropathy followed by secondary uremia. Anyway, secondary uremia caused by obstructive uropathy and stop of urine derivation are frequent cause of death of those with genito-urinary tumors (cervix of the uterus, prostate, bladder, ovary) (1).

Patho-anatomic bases of obstructive uropathy are the most frequently presented by extramural compression or direct ureter invasion of primary localized advanced tumor in small pelvis and/or retroperitoneum (lymph nodes metastases). The final result of obstructive uropathy is hydropneumohletic atrophy, renal insufficiency and uremia.

Diagnosis and management of genitourinary emergencies in cancer patients require a meticulous history, physical examination, as well as radiologic, laboratory, endoscopic and histopathologic examinations.

The clinical features of obstructive uropathy are urinary retention, lumbal or beck pain, hematuria, chills and fever. The laboratory findings of obstruction may be hematuria, pyuria, proteinuria, elevated blood urea nitrogen, creatinine, serum phosphorous and serum potassium. These laboratory findings indicate the possibility of an obstruction leading to renal failure but not to precise diagnosis. The catheterization of urinary bladder, ultrasound examination of urinary tract, excretory urogram, radioisotopic renogram, computerized tomography of abdomen, indicated urinal retention as well as level and the cause of obstruction.

Although the immediate release of obstruction is essential, the intactness of the urinary tract and complete recovery from the obstruction is dependent on definitive treatment of the cancer. Without the treatment, bilateral urethral obstruction progresses and these patients die of uremia. Because of that, it is physician’s responsibility to help the patient and her/his family makes appropriate decision concerning aggressive or conservative therapy.

Since death caused by uremia is painless and is considered human (2,3), aggressive therapy of acute obstructive uropathy is not always the best choice for a patient. Conservative therapy allows dignified dying to a patient with a limited life expectancy and poor quality of life. Patients who have exhausted all primary treatments and cannot improve their functional status should not be considered for aggressive therapy (4). Because of that, development of uremia in these groups of cancer patients can be considered a welcomed event.

Aggressive treatment of obstructive uropathy is favorable for the patients who may benefit from chemotherapy and/or radiotherapy (tumors of testis, Hodgkin disease, carcinoma of the cervix uteri) and all patients who need additional times for evaluation of etiology of ureteral obstruction (there are no sign of progression of underlying disease (5,6).

Urologists and/or intervening radiologists take part in aggressive elimination of obstructive uropathy, and their inclusion in the treatment often depend on cause and level of urinary tract obstruction (lower or upper urinary tract). The obstruction in the lower urinary tract may be temporary controlled by passage of an indwelling urethral catheter. If it is not possible, urinary stent, suprapubic cystostomy or cutaneous vesicostomy may be necessary (7).

Urology and radiology literature is flooded with reports on benefits of percutaneous nephrostomy (PCN) performed under sonographic or radioscopic control (8,9) as a method of urine supravesical derivation from the time of Goodwin’s description of this technique (1955), Mann’s report in 1980 on benefits of this method in the patients with gynecological malignancies (10). A twenty - year experience in performing PCN made this method a method of choice in elimination tumor - related bilateral ureteral obstruction especially of gynecologic localization (11).

Apart from its performing simplicity, low price and minimal morbidity, PCN improved survival rate of patients with malignant disease, but at the same time, it also enable non-critical performance of this method. Many patients who were not suitable for PCN become “nephrostomy cripples”, with prolonged agony caused by existing malignancy. Also, there is no improvement of already poor quality of life (12).

Although simple for performing, this method is followed by complications (hematuria, poor functioning, urosepsis, and accidental replacing) which significantly increased treatment cost, consume health care hours, as well as total morbidity. Therefore, decision on PCN should be made without hurry, considering existing state of the disease, stage of the disease, and expected survival improvement after specific anti-cancer therapy. Several retrospective studies on PCN indicated five independent factors considered absolute contraindications for PCN performing: progression of disease during or immediately after the optimal therapy, inability to apply useful therapy, WHO performance status 2 or lower (3-4), presence of tumor-related problems which endanger life of patient and uncontrolled pain during the optimal medicamentous therapy (13,14).

Literature date and our own experience show that the biggest number of poorly planned PCN has been performed just in absence of good communication among the oncologist, intervening radiologist and/or urologist. Based on quoted above, we may conclude that decision on PCN must be made by a team with obligatory, all inclusive oncology viewing of the problem regarding to elimination of obstructive uropathy caused by malignant disease (15).

REFERENCES

Tumor-induced hypercalcaemia (TIH) is the most common metabolic disorder related to cancer. It occurs in about 10% of cancer patients some time during the course of their disease, mostly in advanced stages. About 50% of all cases of hypercalcaemia are caused by malignancies, most often by myeloma, breast, lung and renal cancers.

The cause of hypercalcaemia is always the increased osteoclastic bone resorption, as the consequence of either local production of cytokines due to bone metastases, or humoral factors secreted by tumor cells. The increased loss of calcium by urine, the decreased glomerular filtration rate and/or increased tubular reabsorption, are the commonest consequences, leading to the oliguria, further rise in serum calcium, and a circles of events that would never recover spontaneously (1). The unrecognized TIH would obviously lead to the terminal stage of malignant disease and death. Since the treatment could be successful, in terms of inhibition of bone resorption, it is important to screen the serum calcium levels in advanced cancer patients at risk for TIH, and to monitor the early signs of hypercalcaemia, as well.

Clinical signs of hypercalcaemia are not necessarily correlated to the level of increase in serum calcaemia. However, fatigue, mild nausea and constipation are the most frequent initial symptoms. Lethargy, confusion, psychotic reactions could rise the suspicion to the metastatic spread into the brain. Dehydration and cardiovascular disorders usually develop late. The diagnosis can be made only by biochemical test. The symptoms of underlying malignancy usually interfere, and complicate the diagnosis. However, the sudden progressive deterioration of the overall condition, coincidental with the disease progression, especially when bone metastases are developing, should suggest the possibility of TIH.

It is not known why an individual tumor begins to secrete osteoclast activating factors. However, it was noted that TIH was often related to the aggressive tumor growth, and in particular to the occurrence of bone metastases. In our study of TIH, 37/38 consecutive breast cancer (BC...
patients with TIH had evolutive bone metastases (2). It is reasonable to suppose that the effective treatment of the malignancy might be the best therapy of TIH. Since the effective treatment option do not exist for most of the malignancies, or their effect can be delayed, as in the case of endocrine treatment, it is necessary to interrupt the osteoclast bone resorption.

The treatment of acute TIH consists of rehydration during 2-3 days to normalize the renal function, and to induce the calciuresis. Loop diuretics are often used to avoid overloading with fluid. The next step is the use of bisphosphonates, Disodium pamidronate (Aredia®) being most effective one, 60-90 mg in a 2-4h intravenous infusion, either in a single or divided doses. Normalization of serum calcium level occurs in the next few days. In our study, median time to serum calcium normalization was 4 days, and it was observed in 28/38 (74%) patients (2). In addition, 15% of patients responded partially (decrease of serum calcium level near to normal value), and 10% failed to respond. The new anticancer treatment was applied in the most patients. Recurrent TIH was related to the failure to anticancer treatment, i.e. to the rapid progression of osteolytic metastases. The next episode of TIH was observed in 7 patients during the next bone relapse. Thus, we found that the effective anticancer treatment is necessary for maintaining the normal calcaemia. In a previous case report, it was shown that even radiotherapy could be effective against the production of osteoclast activating factors (3). Corticosteroids and calcitonin can be used in case of ineffective treatment with bisphosphonates; however, the response is less frequent.

Hypercalcaemia is rarely seen as the manifestation of tumor-flare phenomenon, as the response to anti-estrogen (4). There is no consensus for the approach. It would be reasonable to temporarily stop the endocrine treatment, to treat the hypercalcaemia, and then to re-introduce the anti-estrogen, since the tumor-flare usually predicts the favorable response.

Since the hypercalcaemia is the acute, life-threatening complication in metastatic malignancies, involving bones in a vast majority of cases, the prevention of hypercalcaemia arises as the attractive possibility. A number of clinical studies have been conducted to confirm the benefit from bisphosphonates’ use in the prevention of hypercalcaemia (and other skeletal-related events) in metastatic BC patients. It was found that bisphosphonates could significantly reduce all skeletal complications, including hypercalcaemia, in terms of its decreased frequency and increased time-to-occurrence, in BC patients with osteolytic bone metastases (5). Reviewing the evidences for such a role of bisphosphonates in breast cancer, ASCO Panel of Experts recommended the routine use of two bisphosphonates, pamidronate and clodronate, in BC patients with metastatic bone involvement (6). In the adjuvant setting, however, the role of bisphosphonates in prevention of bone relapses, and thus indirectly in prevention of TIH, remains controversial, although many studies are ongoing.

In conclusion, the early diagnosis of TIH is simple, by the monitoring the serum calcium level in patients at risk. The urgent therapeutic intervention can prevent the irreversible disorders of osteolytic metastases, and allow the potentially effective anti-cancer treatment. Thus, the treatment of TIH, although belongs to the palliative and supportive approaches, can influence the overall survival, at least in some patients with advanced malignant diseases.

REFERENCES

Disseminated Intravascular Coagulation (DIC) - consumptive thrombohemorrhagic disorder in malignant diseases

Key words: DIC; Cancer; Infection

DIC is not an independent disease entity, but rather a pathologic syndrome associated with specific clinical disorders. Clinically, the incidence of thromboembolic events in cancer patients has been reported to vary between 1 - 11%. However, autopsy series showed even higher rates (575%), depending on the tumor type (1).

Thrombotic episodes may precede the diagnosis of cancer by months or years thus representing a potential marker for occult malignancy (2) or may herald relapse or progressive disease (10).

Etiopathogenesis

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Thrombotic episodes may precede the diagnosis of cancer by months or years thus representing a potential marker for occult malignancy (2) or may herald relapse or progressive disease (10).

DIC is a serious complication and the oncology patient may develop this syndrome either as a consequence of the neoplasm itself or as a complication of the treatment of the disease (1).

Cancer may cause DIC in several ways:

- Tissue factor pathway (extrinsic pathway)
- Intrinsic pathway
- By neoplasms itself.

Extrinsic pathway. The most common initiator of this coagulation cascade is thought to be activation of the tissue-plasma-platelet system via the extrinsic pathway of coagulation, mediated by tissue factor previously called thromboplastin. Tissue factor is present in various normal cells as an integral membrane protein receptor for factor VII, which interacts and activates circulating factor VII. Normal host tissues may express procoagulant activity in response to the tumor. Malignancies induce inflammatory reactions that result in activated mononuclear cells that express tissue factor on their surfaces. This phenomenon may be related to tumor adhesion or metastasis.

The intrinsic pathway is also activated, via endotoxin and antigen-antibody complexes that can expose collagen and activate factor XII. Neovascularization of the tumor with an abnormal epithelial lining may activate coagulation. An important mediator of tumor angiogenesis is vascular endothelial growth factor (VEGF). VEGF has been demonstrated in a number of human cancer cell lines, as well as in clinical specimens of breast, brain, ovarian, and colon cancer, suggesting a trophic role for VEGF in supporting tumor growth via host angiogenesis (3).

Direct endothelial damage can also occur, mediated by endotoxin, tumor necrosis factor, and interleukin-1.

Some intact tumorous cells may express or release procoagulant activities, such as tissue factor (TF), cancer procoagulant (CP), prothrombinase activators, platelet activators, tissue-specific proteases, cytokines, and plasminogen activator inhibitors (PAI). Cancer procoagulant is a specific tumor marker absent in normal cells, which directly activates factor X in a vitamin K-dependent manner and inactivates protein S. Proteases (trypsin, cathepsins, elastases, proteinases) may be responsible for the cleavage of various substrates including coagulation factors. Some cytokines (IL-1B, TNFα, IL-6, IL-8) produced directly by malignant cells, or indirectly by mature normal cells, may activate endothelial cells to express procoagulant characteristics (TF secretion, PAI-1 secretion, and thrombomodulin down-regulation). TNF stimulates production of platelet-activating factor, inhibits thrombomodulin expression on the cell surface and is involved in the down-regulation of tissue plasminogen activator. Direct or indirect PAI secretion will accentuate hypercoagulability through the down-regulation of the fibrinolytic system. PAI also stimulates both angiogenesis and tumor invasion (4).

The relative contribution of each procoagulant mechanism varies between tumor cell types and may vary during the clinical course of a single tumor. This includes vascular stasis caused by obstruction of blood flow.

Cytokine release, acute phase reaction and neovascularization may contribute, in cancer patients, to in vivo clotting activation, which is well documented by several plasmatic markers of a hypercoagulable state (2).

Finally, an increased risk for developing DIC has been reported in cancer patient with febrile neutropenia and/or treated with chemotherapy or chemo-hormonal therapy.

The usual treatments for cancer significantly increase the risk of thrombotic events or DIC. Deep vein thrombosis and pulmonary embolism are the most common thrombotic events associated with antineoplastic therapy (tamoxifen along with other agents), but cerebral vein thrombosis and thrombotic microangiopathies can also be seen. High-dose chemotherapy and bone marrow transplantation is associated with enhanced risk of hepatic veno-occlusive disease (VOD). A high risk of thrombosis was noted in patients treated with cyclophosphamide, methotrexate, fluorouracil and vincristine, mitomycin C. Possible explanations for these chemotherapy-induced abnormalities include impairment of vitamin K metabolism and inhibition of DNA/RNA synthesis, leading to a reduction in protein synthesis by the liver. In addition, endothelial cell injury can lead to quantitative or qualitative abnormalities in von Willebrand factor (vWF) which can enhance the thrombotic potential. Other possible mechanisms include direct platelet activation, reduced fibrinolytic activity, and the release of procoagulant from tumor cells dying as a result of antineoplastic therapy (5).

In febrile neutropenia infection with a wide variety of gram-positive and gram-negative organisms has been reported to participate DIC. Bacterial endotoxin can activate factor XII, induce platelet release reaction, cause endothelial sloughing, induce release of TNF, or start a release of granulocyte procoagulant materials. In response to bacterial lipopolysaccharide (LPS), monocytes transcribe, synthesize, and express TF on their surface, thereby conveying to activated monocytes the ability to initiate the
blood coagulation protease cascades (6). The bacterial mucopolysaccharide of gram-positive bacteria may induce DIC by a similar mechanism (7). Viremia with CMV, hepatitis B virus, or human immunodeficiency virus can also initiate DIC. The mechanism may be antigen-antibody associated activation of factor XII, a platelet release reaction, or endothelial damage (8). Direct endothelial damage can also occur, mediated by endotoxin, tumor necrosis factor, IL-1, platelet-activating factor, and complement, which leads to further release of tissue thromboplastin and tissue factor.

Intravascular hemolysis, whether massive or mild, may trigger DIC via the release of red cell adenosine diphosphate (ADP) or red cell membrane phospholipidoprotein (9).

These effects result in activation of local microvascular coagulation.

Once DIC is initiated, the underlying biochemical events and pathophysiology are essentially the same in various disease states. With any individual cause of DIC, the coagulation disorder is more pronounced if complicated by hypotension, acidosis, hypoxemia or shock (9).

**DIAGNOSIS**

**Clinical findings**

There are no clinical findings specifically diagnostic for DIC. DIC or consumption disease is a thrombotic disease that is due to overactivation of the coagulation cascade. The clinical manifestations may be those of thrombosis or hemorrhage, secondary to the consumption of coagulation factors and platelets. The first association between cancer and thromboembolic events was noticed by A. Trousseau, 1865 (10).

DIC begins as localized microvascular coagulation. Depending on different organ involvement with microvascular thrombotic lesions (brain, kidney, gastrointestinal tract, eye, liver, skin...) DIC is described as Hemolytic-uremic syndrome HUS), ileus, scintillation, veno-occlusive disease (VOD), neurologic disturbances, petechiae, purpura ecchymoses, acral cyanosis (Raynaud's phenomenon, if cisplatin-bleomycin regimen is used). Systemic manifestation of thrombohemorrhagic syndrome is described as thrombotic thrombocytopenic purpura (TTP) (11). And finally, the best description of clinical manifestations in acute DIC is described by Little 1911, known as Waterhouse-Friderichsen's syndrome.

**Laboratory analyses**

Usual coagulation screening tests are not specific for DIC (PT, PTT, and TT). Other tests of hemostasis have been reported to be abnormal in patients with DIC. Included in this group are assays: platelet factor-4 (PF 4), beta thromboglobulin, fibrinopeptide A (F A), prothrombin fragment F1+2, activated protein C-sensitivity ratio (aPC-SR), and the fibrin degradation peptide B-beta 15-42. These tests may be of value in the recognition of subclinical activation of coagulation in some patients with malignancy (1).

Laboratory findings in the chronic or compensated form of DIC differ from those in acute fulminant DIC. The platelet count may be near normal or normal, PT and PTT are commonly normal or shortened. DIC is always elevated. Red cell fragments (schizocytes) are present in most patients (1).

In acute DIC majority of the laboratory tests are abnormal. There is no single "gold standard" laboratory test, but used in appropriate combinations, laboratory tests can clarify the coagulation status.

Chronologically, in the first step prothrombin fragment F1+2, TAT, and Fibrinopeptide A and B are elevated, may occur thrombocytopenia. PT, PTT, TT are normal or shortened. Clinical signs are absent. Low platelet count diagnostic value is quite limited, especially in cancer patients receiving chemotherapy.

In the second step decreases functional level of ATIII (<80%), PT, PTT and TT are normal and D-dimmer occurs. D-dimmer is formed when plasmin digests cross-linked fibrin, not fibrinogen. Therefore, the D-dimmer test appears to be the most reliable test in acute DIC if there is no elevated level of PAI. If a PAI level is elevated, only decreased level of functional AT III may suggest a presence of DIC. In the next step PT, PTT and TT may be prolonged. Obviously, the PT and PTT are of limited usefulness in acute DIC. Measurement of clotting factor levels is not recommended. In all steps the euglobulin clot lysis time is normal. In the last step of DIC when appears secondary fibrinolysis euglobulin clot lysis time is shortened.

**Treatment of DIC**

Treatment of DIC in oncological patients is always directed to the underlying disease. With aggressive individualized treatment of DIC, survival rates as high as 76% have been reported in patients with fulminant DIC (12).

Treatment should be triggered by symptoms of the coagulopathy, but exception includes incipient tumor lysis syndrome. The symptom complexes that usually required therapy are venous thrombosis (deep venous thrombosis or the Trousseau syndrome), arterial thrombosis, and hemorrhage. The treatment includes:

- Anticoagulant therapy
- Transfusion component therapy
- Antifibrinolytic therapy

**Anticoagulant therapy**

Heparin, with the dose adjusted to prolong the aPTT from 60 to 90 seconds (1.5X-2X control). Frequently, the administration of heparin normalizes other abnormalities, such as high fibrin degradation product levels (FDP; D-D) and low platelet counts. The basis for using heparin is the control the intravascular coagulation, which is the initial step in DIC. Even if the patient is bleeding from secondary fibrinolysis, the intent is to control the microvascular thrombosis and subsequent multiple organ damage, and stem the stimulus for secondary fibrinolysis.

Two types of heparin are available for use: unfractionated (UH) and low-molecular-weight (LMWH).

LMWH is associated with less bleeding than UH and has little effect upon platelet function.

Heparin requires for its activity AT III at levels more than 80%. In DIC also natural coagulation inhibitors like AT III are consumed, producing relative resistance to heparin therapy. For this reason some authors advise to substitute it for ATIII.

**Blood component transfusion**

Significant clinical hemorrhage should be treated with the appropriate blood product.

Laboratory "triggers" for blood component transfusion in DIC patients include (13):

**Cryoprecipitate** is enriched in fibrinogen and factor VIII, and should be used for fibrinogen levels <1 g/l or 0.75 g/l.

**Fresh frozen plasma** (FFP) contains 1 unit/ml of all clotting factors, AT III and should be used if the fibrinogen level is above 1 g/l and PT/PTT is still prolonged >1.5 x control or if the AT III <80%.

**Platelet concentrates** for platelet counts of <50 x 10^9/l. In spite of these criteria in acute DIC, where there is bleeding associated with thrombocytopenia, platelet transfusions should be given in addition to coagulation factor replacement. In chronic DIC, or in the absence of bleeding, platelet transfusions have nonclinical advantages and should not be given merely to correct abnormal laboratory results (13).

If clotting factors are being consumed rapidly and the patient is hem-
or hemorrhaging, blood products are given concomitantly with low dose heparin (15,000 U/24 hour) (14,1). Heparin is needed to block thrombin generation and to reduce the use of blood products. Blood component replacement therapy "fuels the fire" of DIC. This situation occurs most commonly in patients with widespread carcinoma complicated by tumor cell emboli in the microvasculature (1).

**Antithrombin III (AT III)** concentrates may be effective therapeutic option in patients with decreased level of AT III in acute DIC.

Antifibrinolytic agents (epsilon-aminocaproic-acid EACA, Aprotinin) are dangerous in DIC because of the propensity to worsen thrombosis (1). It is important to distinguish between DIC with secondary fibrinolysis and systemic (primary) fibrino(gen)lysis in patients with the del fibrinolysis syndrome. Systemic fibrino(gen)lysis is caused by the entry of profibrinolytic enzymes into the circulation, and is most commonly found in patients with late-stage prostatic carcinoma. The two entities, DIC and systemic fibrinolysis, can usually be quickly separated using relatively simple and widely available laboratory assays. The best tests to use in this situation are the euglobulin clot lysis time and an assay of circulating antiplasmin. A short lysis time (<60 minutes) and antiplasmin levels of <30% suggest the presence of systemic fibrinolysis and raise the possibility of treatment DIC with systemic antifibrinolytic agents, which are usually given in coherence with heparin. Even though bleeding is the major clinical problem in these instances, low-dose heparin is recommended to inhibit activated thrombin activity. EACA used alone in DIC has been associated with catastrophic thrombosis (15).

**Other therapies**

Tissue factor pathway inhibitor (TFPI)
Activated protein C (APC)
Anti-tumor necrosis factor antibodies
Hirudin (thrombin inhibitor highly specific for thrombin)
Antibodies to the endothelial leukocyte adhesion molecule
Anisodamine (inhibitor of an ADP-induced platelet aggregation)

**Prophylaxis**

Patients found to have modest increases in D-dimer levels are at high risk for thromboembolism and DIC following surgery, chemotherapy, hormone therapy or prolonged bed rests, so that prophylaxis (with heparin, low-molecular-weight heparin, or warfarin) is often warranted. For prevention of thromboembolism and DIC during chemotherapy is recommended LMWH (dalteparin sodium at 2500IU daily) (16) and very-low dose warfarin for 6 weeks. The warfarin is adjusted to maintain an international normalized ratio (INR) between 1.3 and 1.9 (17), or close to 2.0 (20).

Chronic DIC (compensated DIC), with only a minor bleeding tendency, may be treated with anti platelet agents such as aspirin or dipyridamole if the underlying cause (such as disseminated malignancy) is not treatable (12).

Last, but not least, a direct pathogenetic role of clotting activation in the progression of malignancy has been repeatedly proposed on the basis of pharmacological studies with anticoagulant/fibrinolytic drugs in experimental animals and selected clinical malignancies (2). In solid tumors, CP, a vitamin K dependent enzyme could represent the selective target of the anti-metastatic effects of warfarin treatment (2). Inhibition of tumor-secreted VEGF limits primary tumor growth by inhibiting angiogenesis; Anti-VEGF antibodies inhibit a later stage of experimental metastasis (18).

Angiostatin, a proteolytic fragment of plasminogen appears to be a possible anti-cancer drug, specifically blocking angiogenesis (19).

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Opportunistic infections in cancer patients: can they make an emergency in oncology? A ten-year survey of isolates in our protected unit

Key words: Opportunistic infections; Malignancy

The patients with cancer may be immunocompromised because of the underlying malignancy or the antineoplastic therapy. Specific malignancies may be associated with immune deficits that predispose to infection with particular pathogens. Therapeutic modalities such as cytotoxic chemotherapy, corticosteroids and localized or widespread irradiation result in additional deficiencies of host defense. The consequence of these interrelated abnormalities of immune function is the immunocompromised cancer patient.

Unperturbed, the endogenous microbial flora exists as a carefully balanced, synergistic microenvironment within the host. In healthy persons the immune system is working correctly controlling these germs. In immunocompromised cancer patients pathogens which rarely cause disease under routine circumstances, often get out of control and cause serious infections. Those infections that take advantage of weakness in the immune defenses are called “opportunistic”. Among cancer patients who are subjected to extreme degrees of immunosuppression, almost any type of bacterial, fungal, viral, protozoal, or parasitic organism can exhibit pathogenic potential and lead to devastating consequences for the host. Furthermore, patients who have experienced one opportunistic infection are at great risk of developing a second one. In these situations, particularly during the period of neutropenia, when infections are not necessarily manifested by a clear symptomatology, and when the onset of septic shock can be rapid and surprising, the life-threatening opportunistic infections perform emergency in oncology (1, 2).

At Medical Oncology Department of Institute for Oncology and Radiology of Serbia, in a three-year period (01.01.98-31.10.00) 129 blood cultures positive for bacteria and yeasts were isolated: 59 in 1998, 46 in 1999 and 24 in 2000. The most common organisms were Staphylococcus epidermidis (40%), E. coli (10,8%), Pseudomonas aeruginosa (7,7%), Staphylococcus pyogenes (7%), Streptococcus α haemoliticus (7%) and Acinetobacter calcoaceticus (3%). Thus, P. aeruginosa and A. calcoaceticus were found to be the most frequently isolated opportunistic pathogens. In addition, a number of unusual opportunistic organisms were identified which could be peculiar to the bacteriologically protected unit (Table 1).

<table>
<thead>
<tr>
<th>Opportunistic pathogen</th>
<th>N° of isolates</th>
<th>Percentage</th>
<th>Lethal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>10</td>
<td>7.7%</td>
<td>4</td>
</tr>
<tr>
<td>Acinetobacter calcoaceticus</td>
<td>4</td>
<td>3.1%</td>
<td>1</td>
</tr>
<tr>
<td>Corynebacterium jeikeium</td>
<td>1</td>
<td>0.8%</td>
<td>1</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>1</td>
<td>0.8%</td>
<td>0</td>
</tr>
<tr>
<td>Pseudomonas cepacia</td>
<td>1</td>
<td>0.8%</td>
<td>0</td>
</tr>
<tr>
<td>Salmonella enteritis</td>
<td>1</td>
<td>0.8%</td>
<td>1</td>
</tr>
<tr>
<td><strong>Σ</strong></td>
<td><strong>18</strong></td>
<td><strong>14%</strong></td>
<td><strong>7</strong></td>
</tr>
</tbody>
</table>

* Total number of positive isolates 129

Concerning opportunistic pathogens among bacteria, P. aeruginosa has emerged as a major problem in cancer patients undergoing chemotherapy. Four out of ten patients with pseudomonas sepsis have died. Clinically, all of them had septic shock. For two of them we presume an imported infection, and two where considered as nosocomial infections. Air condition was the proven source of nosocomial infection in the room were two patients died due to P. aeruginosisa septicemia in two months period. Only in one patient with lethal outcome, multiply - resistant P. aeruginosasa isolate was found, while in the others, antibiograms demonstrated sensitivity to majority of tested antibiotics (3).

In a three-year period, A. calcoaceticus was isolated in 4 blood cultures. All four patients had severe chemotherapy - related myelotoxicity with febrile neutropenia. Bacteraemia with an A. calcoaceticus lead to fatal outcome in one out of four patients. Results of antibiograms demonstrated resistance of A. calcoaceticus to most of the antibiotics tested, but the clinical efficacy of the antibiotic regimens used was satisfactory, with three completely recovering patients.

Fungal infections are also important opportunistic infections in immunocompromised cancer patients. Early diagnosis is difficult and the prognosis is usually poor. Among all positive blood cultures, only one fungemia with Candida famata in patient with lung cancer was detected, presumed non-nosocomial infection. The patient recovered when aggressive antifungal therapy was applied.

This retrospective survey of the most frequent opportunistic bacterial and yeast pathogens identified during the last three years shows a decreasing trend of incidence compared with previous years figures (where available), especially concerning intrahospital infections. This is probably due to improved measures of bacteriological protection and control in intensive care unit (4).

In immunocompromised cancer patients with neutropenia caused by either the disease itself or the applied therapy, CMV infection can cause serious clinical disorders. With immunosuppression, reactivation of a latent CMV infection can occur or in some cases re-infection with different types of CMV can manifest. From 08.01.1990 to 14.06.1993 prevalence of CMV antibody findings were investigated in 454 patients with malignant lymphoma and metastatic solid tumors undergoing chemotherapy. Out of 454 patients, 398 (87,7%) were reactive to CMV while 56/454 (12,3%) were not reactive to CMV. Positive seroconversion was found in 15/56 (26,8%). In 22/454 (4,8%) patients, IgM antibodies were found, while both IgG and IgM antibodies were found in 16 of those 22 patients. This finding is an indication of a primary infection. Five patients developed IgM antibodies after the positive detection of IgG antibodies, which points to reactivation.
improve the outcome of these often life-threatening infections. As immunosuppressed patients represent the population at the greatest risk for Toxoplasma gondii infection, a major opportunistic pathogen among parasitic infections, malignant diseases and the chemotherapy used for their treatment could possibly induce reactivation of chronic T. gondii infection. During the period between 01.01.1990 and 01.10.1991, 395 sera samples from 143 patients with a confirmed diagnosis of malignant disease (lymphomas 134, solid tumors 9) were analysed for toxoplasma antibodies. 55 (38%) patients were seronegative, and 87 (61%) patients had positive T. gondii specific IgG with negative IgM antibodies (latent infection). Only in one patient both classes of T. gondii specific antibodies were detected. This patient was treated for non-Hodgkin lymphoma, and also had a positive HIV-1 serology (AIDS). One patient had detectable both IgG and IgM antibodies in the first serum sample, but in the two consecutive samples T. gondii specific IgM antibodies were negative, suggesting a possible transition of acute to chronic infection. In both patients with positive Toxoplasma IgM antibodies there were no clinical symptoms which could be related to any form of acute toxoplasmosis. Seroconversion was not detected in any of the seronegative patients. In our experience, the reactivation of latent toxoplasmosis in patients with malignant disease, particularly lymphomas, treated with chemotherapy, was not detected; we thus conclude that T. gondii de novo infection or reactivation is not a major hazard for patients with neoplastic disorders outside the context of AIDS and transplantation procedures.

Immunocompromised, chemotherapy-treated cancer patients are very susceptible to all types of infections, especially with opportunistic microorganisms. Of critical importance is that opportunistic infections are associated with high rates of morbidity and mortality in immunosuppressed cancer patients. Therefore, it is suggested for medical oncologists to become familiar with the modalities currently available to diagnose opportunistic infections in immunocompromised cancer patients. Wiad Lek 1998;51(Suppl.4):300-3.

Toxoplasma IgM antibodies there were no clinical symptoms which could be related to any form of acute toxoplasmosis. Seroconversion was not detected in any of the seronegative patients. In our experience, the reactivation of latent toxoplasmosis in patients with malignant disease, particularly lymphomas, treated with chemotherapy, was not detected; we thus conclude that T. gondii de novo infection or reactivation is not a major hazard for patients with neoplastic disorders outside the context of AIDS and transplantation procedures (6).

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Radiation enteropathy - Syndrome "Grelle radique"-

Key words: Irradiation treatment; Intestinal complications

The gastrointestinal complications of radiation therapy are complex. Walsh first describes radiation enteritis, syndrome of "grelle radique" French authors, in 1897 (1). Radiodermatitis in 75% of cases is the result of radiation treatment for cervical or endometrial carcinomas. The radiotherapy for cancer of the rectum, prostate, bladder, ovary and for lymphoma also can cause enteritis. Small bowel injury accounts for 30 to 50% of all severe radiation injuries (2). The toxicity of radiation therapy is dose related. The frequency of complications from pelvic irradiation is directly related to the absorbed dose of radiation. Radiation induced intestinal injury may be acute, usually limited and reversible, and affect 75% of all irradiated patients. Chronic abnormality may appear after a latent period from six months to 30 years (3). The incidence of radiation enteritis is difficult to determine: many patients may have subclinical course. Asymptomatic patients have subclinical malabsorption.

In 5 to 25% of patients, they had symptoms of radiation enteritis and 2 to 5% required operative intervention (4). Relatively immobile intestinal segments, such as the terminal ileum and rectum, or which become immobile due to postoperative adhesions are more susceptible to radiation injury. Also, radiation injury produces an endarteritis. These effects are caused both by external and intracavitary application. Combination with chemotherapy produces more damage than...
either modality alone.

Acute effects of irradiation mostly affect intestinal mucosa and blood vessel endothelium. Intestinal mucosa changes result in malabsorption. Acute effect is reversible. Cellular damages in rapid cell proliferation tissue either tumor or normal are based on DNA changes.

In chronic phase, changes on endothelial cells of the small submucosal arterioles undergo further degeneration. Vascular thrombosis leads to an obliterate endarteritis and endophlebitis, producing ischemic changes, ulceration and necrosis. Intestinal bacteria invade necrotic tissue and cause further damage resulting with strictures, ulceration, perforations and fistula (5).

Diagnosis is complex and includes endoscopy, contrast x-ray examination, CT of abdomen, Doppler ultrasonography of blood vessels, as well as, other non-invasive and invasive procedures.

In respect to changes in acute and chronic phase it is necessary to distinguish radiation enteropathy from progression of malignant disease. The treatment has to be planed according to pathology and pathophysiology substrates.

Nonoperative management includes symptomatic treatment of malabsorption and recovery of mucosa damages. This can be achieved by correction of water and electrolyte disbalance, antispasmodic and anticholinergic drugs, and elemental diet. Rectal bleeding can be treated with YAG laser.

Operative treatment is usually reserved for patients who either are unresponsive to medical treatment or present an emergency. They may have an intestinal obstruction, fistula, massive rectal bleeding and peritonitis. Most are in critical condition, malnourished, debilitated and immunodeficient. Such patients need rigorous supportive measures, including preoperative total parenteral nutrition (TPN).

Mechanical occlusion is usually on four distal ileal loops. Some surgeons favor bypass technique and some prefer resection of the obstructed segment and anastomosis of healthy bowel. The trend is toward more extensive excisions and normal bowel anastomosis because of high risk of dehiscence.

Frozen-section specimen taken from sites for anastomosis may help identify radiation damage (6). Anastomosis in terminal ileum and cecum should be avoided. There is still controversy on types of anastomosis. Stapling is usually avoided (7).

Large bowel obstruction usually involves rectosigmoid. The first is decompression of obstructed bowel with derivative colostomy, preferably transverse colostomy. Later, the patient may have resection and anastomosis.

The fistula from irradiated bowel is usually either colovaginal or colovesical. The proximal colostomy is necessary. The colostomy should be maintained for many months, to allow necrosis to disappear. In reconstruction of fistulas muscle or omental flaps are usually used. For rectovaginal fistula the approach is abdominoperineal. For rectovesical fistula, an ileal conduit should be considered. Ileaeile, ileocolonic, and enteroenterocutaneous fistulas are treated with either bypass or excision of the affected area.

Necrosis and perforation of the bowel may cause either diffuse peritonitis or localized abscess. Operative treatment is an emergency and includes excision of perforated segment, drainage of the area and proximal colostomy. These operations have high morbidity and mortality rates (8).

In cases of severe proctitis and rectal bleeding, a proximal colostomy is usually reserved for patients who either are unresponsive to medical treatment or present an emergency. They may have an intestinal obstruction, fistula, massive rectal bleeding and peritonitis. Most are in critical condition, malnourished, debilitated and immunodeficient. Such patients need rigorous supportive measures, including preoperative total parenteral nutrition (TPN).

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In cases of severe proctitis and rectal bleeding, a proximal colostomy is the approach of choice. After subsiding of symptoms, Parks’s procedure, Hartman operation or even abdominoperineal resection could be considered. Several surgical techniques are proposed to protect bowel from radiation injury, such as, omental flap, absorbent polyglycolic acid mesh sling and removable “pelvic spacer” (9).

The operated patients are not definitely cured. Radiation enteritis is a progressive disease and may be complicated in immediate postoperative course, as well a year after or as a relapse of malignant disease. They need a life-long follow-up not only because of malignant disease, but also due to disease caused by irradiation.

Many such patients (15-37%) require repeated surgery, while 50% of patients who remain alive at least 1 year after the surgery for radiation injuries have problems related to such injury, complications of surgery, or both (9).

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Empirical antibiotic therapy of febrile neutropenia in cancer patients

Key words: Febrile neutropenia; Antibiotic therapy

Neutropenia is an oncological emergency in cancer patients receiving myelosuppressive chemotherapy. It predisposes the patient to severe and rapidly progressing infection, especially bacterial, but also yeast and fungal, it markedly alters the patient’s inflammatory response, making it difficult to detect the presence of infection. Finally it attenuates the response to antimicrobial therapy (1).

Febrile neutropenia is present when the absolute neutrophil count (ANC) is lower than 0.5 x 10^9/l (or lower than 1.0 x 10^9/l but anticipated to fall below 0.5 x 10^9/l within 24-48h), with an accompanying fever, defined as an oral/axillary temperature higher than 38.50°C in a single observation, or higher than 38°C on two or more observations during a 12h period (2).

Cancer, blood products or medications should not cause fever, and the physician should ascertain if the patient is receiving drugs that mask a febrile response (e.g., steroids, antipyretic containing analgesics).

EVALUATION OF THE FEBRILE NEUTROPENIC PATIENT

Based both on the clinical course and on microbiological data each febrile episode in neutropenic patient is retrospectively classified as: 1) microbiologically documented infection, 2) clinically documented infection or 3) unexplained fever (2). Infection is documented in approximately 60% of febrile neutropenic patients; in remaining 40% fever is without any clinical or microbiological documentation of infection i.e. “unexplained” (3).

The risk for infection is primarily related to the degree and duration of neutropenia. Although the risk is present when ANC falls below 1 x 10^9/l, it is really increased if ANC <0.5 x 10^9/l (“standard” neutropenia), and it is highest when ANC <0.1 x 10^9/l (“profound” neutropenia) (4, 5). In addition to initial ANC, the duration of neutropenia is also critical for clinical outcome and response to antimicrobial therapy: neutropenia lasting 7 days predisposes the patient to greater risk for medical complications and death during neutropenic episode (6, 7).

As neutropenic patient is unable to produce an adequate inflammatory response, any fever that develops during the neutropenic episode should be considered to be due to infection until proven otherwise. The most common sites of infection are: periodontium, sinuses, pharynx, esophagus, colon, perineum including the anus, skin lesions and lungs (8). Specimens for culture should be obtained from all relevant clinical sites and at least two sets of blood cultures should be taken for bacteria and fungi.

Bacteria are responsible for the majority of infections in neutropenic patients. Until two decades ago, aerobic gram-negative bacilli, especially Pseudomonas aeruginosa, Escherichia coli or Klebsiella pneumoniae were the predominant bacteremic isolates. Since the late 1980s, we have witnessed a major shift from gram-negative to gram-positive bacterial pathogens as well as a shift in the relative frequency of individual gram-negative bacillary species, particularly Pseudomonas aeruginosa (9). Nowadays, bacteremia is most frequently due to aerobic gram-positive cocci: coagulase-negative staphylococci (Staphylococcus epidermidis and others), coagulase-positive staphylococci (Staphylococcus aureus) and various strains of streptococci (9). Even if they become less important numerically, gram-negative infections remain of major concern to clinicians, since their course in neutropenic patients can be fulminant and mortality is still in the range of 20-30% (9). Fungi are common causes of secondary infections especially among patients with profound, persistent neutropenia who have received several days of broad-spectrum antibiotics; more than 85% of fungal infections are caused by two genera: Candida and Aspergillus (9). Viral infections are rare in neutropenic patients, without concomitant immunosuppression.

EMPIRICAL ANTIBIOTIC THERAPY

The concept of empirical antibiotic therapy whereby broad-spectrum antibiotics are given as soon as neutropenic patient become febrile has been the single most important advance in the treatment of febrile neutropenia. The combination therapy with an antipseudomonal beta-lactam (a cephalosporin, penicillin or carbapenem) plus an aminoglycoside is the gold standard (8,10). Monotherapy with an antipseudomonal beta-lactam is recently acknowledged to constitute adequate treatment, especially for unexplained fevers without prolonged neutropenia (10). The prospective, randomized phase III study is ongoing at the Institute for Oncology and Radiology of Serbia to evaluate if monotherapy with cefoperazone is as effective as standard combination of cefoperazone with netilmicin. Provided some coverage for streptococcal infection is given, vancomycin is not a necessary part of initial empiric regimen (10, 11). However, in around 30-40% of patients it will be added during the course of neutropenic episode to provide additional gram-positive coverage.

Recently, to models have been validated to identify patients who are at low risk for serious medical complications during febrile neutropenia and who are, therefore suitable for out-patient management (12, 13). Further research in this significant area of supportive care is of a great importance.

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Acute renal failure induced by antineoplastic agents

Key words: Renal failure; Cancer; Chemotherapy

Many cancer patients receive antineoplastic agents at some time during the course of their illness. Some antineoplastic regimens include several agents that have the potential for significant and synergistic nephrotoxicity. As increasing numbers of patients have been treated aggressively with a curative goal, nephrotoxicity has increased. When nephrotoxicity occurs, this may lead to renal insufficiency, ranging from moderate azotemia to advanced uremia. Uremia, with its infections, hemorrhagic, and metabolic complications, imposes a particularly severe burden on the cancer patient.

The nephrotoxicity due to antineoplastic agents may be manifested as acute renal failure, chronic renal failure, or specific tubular dysfunction. Antineoplastic agents such as alkylating agents, antimetabolites, antitumor antibiotics, and biological agents, are outlined in Table 1 (1). These antineoplastic agents may induce nephrotoxicity soon after initiation of therapy or only after long-term administration. The risk of nephrotoxicity varies with each agent. Table 1 summarizes the risk of nephrotoxicity, time of onset, and type of functional impairment produced by each agent.

Table 1. Antineoplastic agents that produce nephrotoxicity

<table>
<thead>
<tr>
<th>Alkylation agents</th>
<th>Antimetabolites</th>
<th>Antitumor antibiotics</th>
<th>Biologic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cisplatin (1a)</td>
<td>1. High-dose M. (1b)</td>
<td>1. Mitomycin (1a)</td>
<td>1. Recombinant interferon alfa and gamma (3a)</td>
</tr>
<tr>
<td>2. Carboplatin (3a)</td>
<td>2. Cytosine arabinoside (3a)</td>
<td>2. Methotrexate (1a)</td>
<td>2. Interleukin-2 (1a)</td>
</tr>
<tr>
<td>3. Cyclophosphamide (3e)</td>
<td>3. High-dose 6-thioguanine (3a)</td>
<td>3. Doxorubicin (3a)</td>
<td>3. Corynebacterium parvum (3a)</td>
</tr>
<tr>
<td>4. Nitrosoureas</td>
<td>4.5-fluorouracil (3a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Streptozotocin (1a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Carmustine (BCNU) (3b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Lomustine (CCNU) (1b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Semustine (Methyl CCNU) (1b)</td>
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</tbody>
</table>

(1) high risk; (2) intermediate risk; (3) low risk; (a) acute renal failure; (b) chronic renal failure; (c) specific tubular dysfunction; (1) nephrotoxicity from long-term administration.

The renal toxicity of certain drugs, such as cisplatin, high-dose methotrexate and interleukin-2 has been associated with acute renal failure.

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A decrease in the incidence of this complication can be attained with an increased awareness of nephrotoxic potential of offending antineoplastic agents, appropriate prophylactic measures, and the clinical settings that predispose to nephrotoxicity.

A cisplatin dose of 50 mg/m² administered either as a single dose or in divided doses over a 4 or 5-day period, produced nephrotoxicity in a significant percentage of patients. The proportion of cisplatin-treated patients who reportedly experience a rise in serum creatinine is large (6% to 30%), but irreversible renal failure is uncommon with good hydration (2). With higher doses and repeated courses of therapy, nephrotoxicity was severe, frequently irreversible, and a major dose-limiting factor (3). A cisplatin nephrotoxicity generally occurs within 2-7 days from the beginning of therapy.

The kidney accumulates and retains platinum to a greater degree than other organs and is the predominant excretory route for cisplatin. Thus it is not surprising that nephrotoxicity is a major cisplatin side effect and that the primary site of nephrotoxicity is the tubule.

The studies employing hydration-diuresis maneuvers indicated that even higher doses of cisplatin may be tolerated without nephrotoxicity(4). Administration of drugs, such as probenecid or tolazoline, may be effective in decreasing the concentration of drug in renal tubular cells by inhibiting its uptake (5). Also, it is possible that patients who subsequently develop cisplatin nephrotoxicity may be identified on the basis of elevated plasma platinum levels early in the course of therapy. It is possible that dose attenuation during cisplatin infusion in these patients will lessen the probability of subsequent nephrotoxicity. Extending the duration of cisplatin infusion may have some influence on decreasing the nephrotoxicity, which occurs when the drug is given as a bolus infusion.

During the past decade (1990-2000), 1438 patients have been treated at our Institute with platinum-containing regimens. Among them only 20 patients (1.4%), developed signs of acute renal failure (ARF), with 17 patients having non-oliguric form, and 3 patients having oliguric form of ARF. No other etiologies for acute renal failure could be identified. Most patients had done well with hydration-therapy (18 patients), and only 2 patients succumbed to irreversible, fatal ARF. Regarding the duration of ARF, 8/20 patients (40%) followed protracted course of ARF with 5 or more days. In this subset of patients, all were males with median age of 59 years (range 22-75 years). All of them had normal pretreatment parameters of renal function. One patient received mono-cisplatin, and other 7 patients received polychemotherapy, with 6 of them receiving conventional doses, and one escalated dose of cisplatin. Main characteristics of these patients have been summarized in Table 2.

Table 2. Main characteristics of our patients

| N  | age | CDDP mg/m² cycle | Serum BUN | Creatinine serum | Creatinine clearance | Electrolyte disbalance | Diuresis/24 h |* |
|----|-----|------------------|-----------|------------------|----------------------|------------------------|--------------|
| 1. | 59  | 60               | Gr. III   | Gr. I            | Gr. II               | +                      | Norm. *      |
| 2. | 63  | 100              | Gr. II    | Gr. II           | Gr. III              | Norm.                 |
| 3. | 22  | 120              | Gr. II    | Gr. II           | Gr. II               | Norm.                 |
| 4. | 58  | 100              | Gr. II    | Gr. I            | Gr. I                | +                      | Norm.        |
| 5. | 58  | 240              | Gr. II    | Gr. II           | Gr. II               | +                      | Norm.        |
| 6. | 53  | 100              | Gr. I     | Gr. II           | Gr. II               | Norm.                 |
| 7. | 62  | 120              | Gr. II    | Gr. II           | Gr. III              | Norm.                 |
| 8. | 75  | 120              | Gr. II    | Gr. II           | Gr. II               | +                      | Norm. *      |

* Irreversible ARF

Our data clearly indicate that although minimal with preventive measures, the risk of cisplatinum - induced ARF exists. Thus the importance of avoiding or minimizing the nephrotoxic effects of antineoplastic agents is apparent. Well-known measures of protecting renal function, mainly adequate hydration and use of loop diuretics, along with careful clinical and biochemical monitoring make an irreversible renal failure uncommon. The role of chemotherapy protectors such as amifostine seems promising.

Careful evaluation of renal function prior to chemotherapy, application of preventive measures with proven efficacy and repeated laboratory tests in short-mid- and long-terms should reduce the frequency of renal complications while preserving or even improving therapeutic effectiveness.

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