

## Review

# Opportunities for up to date treatment of the colorectal cancer

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**Background.** Up to now the basic methods in the treatment of colorectal cancer are surgery, chemo- and radiotherapy. Throughout current years new methods were developed and successfully used in oncology; they consist of application of specific antibodies, the antibody driven enzyme pro-drug treatment, the application of radioimmunoconjugates and the radioimmunoguided surgery.

**Conclusions.** With the applied methods for the treatment of colorectal cancer we prolong a disease-free surviving period, reduce subjective complaints and decrease mortality.

**Key words:** colorectal neoplasms-therapy

## Introduction

The colorectal cancer (CRC) provides great opportunities for challenging the surgeon's skills, as well as for the application of the modern molecular biological and radioimmune methods for its diagnosis and treatment.

The presented review aims to introduce the contemporary state of the problem and the possibilities for the application of some new methods for treatment into the surgical society.

Despite the achievements of the modern clinical oncology the colorectal cancer is diag-

nosed relatively late, i.e. in the advanced clinical stage. The treatment is unsatisfactory. The mortality is high.

The annual mortality in the United Kingdom in 1995 was about 20 000; Italy 7000; in Bulgaria 1400.

The most frequent localisation of the colorectal cancer is the rectal cancer. Its incidence in the Western European countries is 70 / 100 000 population. Many people could be protected from the colorectal cancer by introducing accessible screening methods. Many of the complications of the traditional surgery can be avoided by improving the technical abilities for the operative treatment.

In about 50 % of the patients suffered from the rectal cancer the definitive colostomy is unavoidable. In 2/3 of them it could be avoided by applying the so-called total mesenteric excision (TME) with a modern stapling technology. The early diagnosis, the accurate pre-operative staging, the radical surgical inter-

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vention and the subsequent postoperative chemo- and radiotherapy are of great importance for the complex treatment of the colorectal cancer.

Up to now the literature does not comment the issues about the functional disorders of the reservoir functions and the disturbances of the sexual function and the socialisation of the person.<sup>1</sup>

At present the main methods for the treatment of the colorectal cancer are:

- Surgery
- Chemotherapy
- Radiotherapy

In the recent years the following new technologies and methods are applied for the treatment of the colorectal cancer:

- Application of specific antibodies;
- Creation and application of radioimmunoconjugates;
- Radioimmunoguided surgery (RIGS);
- Antibody driven enzyme pro-drug treatment (ADEPT).<sup>2</sup>

### Application of specific antibodies

The development of immunology and immunotherapy as a branch of the oncology originates from the works of Cooley who established that in patients with the advanced sarcoma the same has a regressive course after a severe infection.

There were hopes due to some medicines, like BCG vaccine, levamisol (Lev), interferon, interlevkin -2 (IL-2). There are several randomised studies for the effect of BCG-vaccine application in patients with CRC but none of them has proved some advantage regarding the total or the disease-free surviving period.

Levamisol increases the immune response by stimulating the T-lymphocytes, the macrophages and the neutrophils. The simultaneous application of Lev+5 Fluorouracil (5-FU) to the patients in stage C, according to Dukes, decreased mortality in 1/3 of the cas-

es. The single use of Levamisol does not cause changes in the percentage of the survival rate compared with the other group of patients who do not receive the medicine.

Another study of the application of IL-2 has found higher percentage of the survival of patients who have received this medicine before the operation, followed by the postoperative application of 5-Fu and Folic acid. There was found that this medicine increased the ability of patients to tolerate easier the postoperatively developed lymphocytopenia.<sup>2,3</sup> The works of Leonard P.C. (1999) and Brivio et al. (1996) claim that the medicines stimulating the humoral immunity do not meet the hopes reposed on them. That is why in the clinical practice the antitumor antibodies (Ab2) were established and introduced. The works in this field are directed to:

- Manipulation of antigen presenting cells;
- Use of co-stimulating molecules for facilitating the specific cell activation;
- Use of double specific antibodies by T-cell targeting to the tumour.

### Monoclonal antibodies

The designing and introducing first in the experiment and later in the clinical practice of monoclonal antibodies is related with the invention of CEA. Its relation with the cancer of the colon has encouraged studies using radio-labelled anti-CEA monoclonal antibodies. Other two classes with even higher specificity are TAG-72 and 17-1A. In a randomised study on 189 patients with CRC, stage C according to Dukes, who have been treated by the resection received either 500 mg 17-1A antibody, followed by 4 x 100mg infusions every month or have been just followed up for 5 years. In the treated group it was found 27% decrease of the relapses and 30% of the mortality.<sup>2,4</sup>

High affinity single-chain Fv antibodies loaded with radioisotope and CEA were cre-

ated in the last 2 - 3 years. They, with high tumour affinity and their sensitivity, significantly exceed this of the up to now used computer tomography (CT).<sup>5</sup>

### Radioimmunoconjugates

The radioimmunotherapy was developed as a type of treatment due to the ability for the successful targeting of radiolabeled antibodies to the tumour antigens (e.g. radioactive CEA antibodies for the treatment of CRC).<sup>2</sup> They are high - energy beta-particles, emitted from Radionuclide, such as <sup>131</sup>I, <sup>90</sup>Yt, <sup>111</sup>In, accumulating in the tumour, characterised with high efficiency in experimental models and for <sup>131</sup>I and <sup>111</sup>In in patients.

### Radioimmunoguided surgery

The implementation of the above-mentioned radioimmunoconjugates in the medical practice contributed to the development and application in the surgical diagnosis of the so-called radioimmunoguided surgery. The postoperatively applied radioimmuno-antibodies are targeted against the tumour tissue. By the aid of a gamma-detector in the particular time interval and even intraoperatively the tumour process can be exactly located and staged. The implementation of the method will facilitate:

- Finding metastases in hepatogastric ligament
- More comprehensive and exact staging of the tumour process.

A problem for the intraoperative staging is whether there are metastatic lymph nodes in hepatogastric ligament or not. The application of anti -TAG - MoAbs changed the decision making for the surgical treatment and staging of patients with primary or relapsing colorectal tumour. There can be concluded that TAG - MoAbs can be used for the intra-

operative detection of the tumour even when there are no significant levels of the serum TAG- 72 and /or CEA.<sup>6</sup>

In the study of Filez L. (1999), carried out on 26 patients with CRC, the application of RIGS has led to the change of the operative technique in 16 patients.<sup>6</sup>

At present in USA and Europe a multicenter clinical trial for the evaluation of the possible benefits of RIGS is going on in patients with the primary colorectal tumour as well as with its relapses.<sup>7</sup>

### Chemotherapy of CRC

Already for several decades 5-Fu the main stream of the treatment of advanced colorectal cancer and of some other solid tissue malignancies is obvious, despite that its success in patients with the advanced colorectal cancer is low (incidence of effectiveness 10-15 % when using bolus injections).

The application of 5-Fu by the infusion has a better effect than the bolus injection due to the route of administration or to the dose intensity achieved or as a combination of both factors.<sup>8-10</sup>

The presence of some new drugs including biochemical modulators of 5-Fu, increasing its cytotoxicity, has renewed the interest to these agents in the recent years.

Some of them are other fluoro-pyrimidins, new modulators of 5-FU or new ingredients, activated in a different way.

*5-Etinoluracil.* At present a clinical trial of this agent in combination with 5-Fu is carried out.

*Trimetrexat.* It is considered as a more potent modulator of 5-Fu than metotrexate. One recently completed phase III clinical trial has found good results in the treatment of patients with CRC.<sup>11-12</sup>

### *Thymidilat - syntetase (TS) inhibitors*

The TS inhibitors catalyse the uridin monophosphate (UMP) methylation to the timidilatmonophosphate (TMP), which is after that metabolised to the timidilatmonophosphate (TTP). At present 6 TS inhibitors are included in the clinical practice as pre-clinical or early clinical trials.

*Tomudex* (ZD 1694 or raltritrexed) is a specific TS inhibitor in the advanced stage of a clinical trial. In a large phase II study 187 patients with the untreated colorectal cancer were included. An objective effect is found in 26 %. In a completed randomised phase III clinical trial comparing Tomudex with 5-Fu+Lev. (bolus injections) the identical survival and degree of effectiveness has been found. Tomudex was been applied in a dose of 3 mg/m<sup>2</sup> as an infusion in every three weeks.

### *Other drugs*

*Irinotecan* is a topoisomerase I inhibitor and it is created for the treatment of the advanced CRC. The DNA-synthetase inhibition leads to a retention of S-phase of the cell cycle. In a trial with the agent on 455 patients with the advanced CRC there was found the stabilisation of the disease in 42 %, benefit incidence of 13 % and symptoms suppression in 62 %.<sup>13,14</sup>

*Oxaliplatin*. This is a diamonohexan platinum complex with an alkylating agent. There was found the benefit incidence of 10 % and in combination with 5-Fu+Lev. of 20-40 %.

### **Prevention of the relapsing CRC**

The incidence of relapse after the radical resection in patients with CRC varies from 2,6 up to 32 %. The time for the local relapse is various but in 55 to 80 % it occurs in the first 2 years following to the operation.<sup>15</sup>

The incomplete tumour resection is one of the causes, as according to different authors it varies from 4 to 27 % as 85 % of the patients have tumour invasion of the lateral resection lines and develop a relapse in a term of 23 months.<sup>15</sup>

According to the data of Burkhardt et al., cited from other authors too<sup>15</sup> by the aid of the conventional histology bone marrow metastases in 17 % of patients with the intestinal cancer without any evidence of the systemic problems were diagnosed.

Except these two widely accepted methods in the recent years there were accepted methods for:

- Intralumen tumour sterilisation by Povidone iodine 10 % or 5 % solution, iertimide, chlorhexidine and Dakin's solution which were assessed as more cytotoxic and cancericide than some other agents.<sup>15</sup>
- Systemic chemotherapy
- Intraportal chemotherapy

Their implementation immediately after the operation causes the destruction of the tumour cells, which could disseminate in the portal circulation at the time of the surgical intervention. The analysis based on the data upon 3824 patients and consistent with the aim of the treatment showed a reduction of the risk for relapse with  $14 \pm 5\%$  ( $p=0,007$ ) and for death with  $13 \pm 6\%$  ( $p=0,007$ ) after median 5 year follow up.<sup>16</sup>

- Intraperitoneal chemotherapy. There is no available data about performed controlled trials.

### **Conclusions**

Reaching high incidence of surgical healing is the most important aim in the present time.

Instead of being considered as "harmless" the abdomino-perineal extirpation should be applied only for the highest situated cancers.

The high specificity of immunotherapy will lead to the effective treatment but will create an immune memory providing a defence against relapses.

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