Therapeutic considerations in Dukes C colon cancer
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Summary and conclusions

Colon cancer is one of the main health issues in the western world. In the Netherlands more than 7000 patients are diagnosed yearly with this disease and half of them will die from it. Prognosis largely depends on tumor stage, which is estimated by radiological, clinical and histological characteristics. After histological research; tumor depth, surgical resection margins and lymph node involvement is assessed. These histo-pathological variables are used in classification systems to estimate the prognosis of the patient. Since Dukes described the first classification system for colorectal tumors in 1932, many other classification systems were introduced like the Astler Coller, modified Dukes, TNM and Jones classification. All these prognostic models are used to assess the individual prognosis of the treated patient. Unfortunately, most of these classification systems are only indicative for a patient’s prognosis. But, a useful and accurate staging system remains the key to a successful oncological treatment. Due to the expanding genetic knowledge of the initiation and development of tumors the development of a staging system that predicts individual prognosis and to use it in daily clinical practice might be possible. Although genetic research expands enormously in the last decade, clinical implications for sporadic colorectal cancer are not yet recognized. In contrast, genetic counseling of patients with Familial Polyposis Colon cancer and Hereditary Non Polyposis Colon Cancer (HNPCC) has lead to clinical implications, primarily by preventive colorectal resection. The future will show if gene-therapy will offer a solution for patients with hereditary colorectal cancer. In chapter II the immunological reaction on a dermal stimulus of Di-Nitro-Chloro-Benzene (DNCB) is presented. The reason for this investigation was based on the renewed interest in the clinical use of levamisole in the treatment of Dukes C colon cancer. Patients with decreased T-cell function have absent skin reactions but if treated with Levamisole, skin tests can be restored to normal indicating restoration of a defective T-cell system. Patients with a normal T-cell system have no immunological reaction on stimulation with Levamisole. After a curative resection of a Dukes C colon cancer, most patients have a normal DNCB skin test. It is hypothesized that only patients with defective T-cell systems, and absent DNCB skin tests, are treated usefully with Levamisole. Adjuvant treatment of patients with Dukes’ C colon cancer is very intensive (patients are treated with 5FU and Levamisole on a weekly basis for a period of 12 months), and a selection of patients who will benefit from adjuvant treatment with Levamisole is
essential. This study started in 1991 and it was thought that the development of an immunological parameter measuring the T-cell system could have clinical use in patients treated with Levamisole. In the seventies DNCB skin tests were used to evaluate the effect of levamisole. A disadvantage of this method was the semi-quantitative character of it. Towards the end of the eighties soluble interleukin 2 receptor (sIL2r) and soluble CD8+ were used to measure T-helper cell function and cytotoxic T-cell function in the evaluation of cancer patients. Clinically, these parameters are primarily used in the evaluation of disease activity in leukemia’s but solid tumors have shown to have abnormal values as well. The combination of a standardized dermal stimulus with DNCB and the reaction of the T-cell system measured by sIL2r and sCD8+ could be used as a more reliable selection tool. Unfortunately, DNCB had no systemic effect on sIL2r and sCD8+ levels in ten patients with advanced colon tumors, although initial levels were increased. It is concluded that the combination of a skin test and simultaneous measurement of sIL2r and sCD8+ cannot be used as an in vivo T-cell test. On the other hand DNCB skin tests and plasma levels of sIL-2r and sCD8 seem to be equally useful and can therefore be used simultaneously in the evaluation of the T-cell system.

In chapter III we report a high frequency of novel variations, including a novel polymorphism, occurring outside the hotspot codons of the KRAS oncogene of which a proportion may be considered as functionally significant mutations. When genetic analysis is performed on colorectal tumors it is essential that tests have a near 100% positive predictive value. This means that if the KRAS gene is changed by mutations the test has to find these mutations in the lab. Former tests focused on codon 12 and 13 only but other codons and splice site junctions can cause significant mutations in the KRAS gene as well. By using DGGE a virtual 100% mutation detection rate could be obtained and with a high sensitivity to detect small amounts of mutant DNA. Along with the frequency of hotspot mutations found in this study, this method demonstrated the usefulness of the described KRAS-DGGE mutation detection system and the appropriateness for future use in KRAS genotyping of colon tumors.

In chapter IV a better method is presented to evaluate the entire TP53 gene. A high frequency of TP53 mutations was found both in the lung cancer cell lines and in paraffin-embedded colorectal carcinomas, including many novel mutations and mutations reported for the first time. In the specific tumor types analyzed, a convincing demonstration of the effectiveness of the described TP53 mutation detection system is given. Concluded is that a large number of the mutations is located outside the evolutionary confined regions and this might indicate that
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former studies presenting TP53 mutations in colon cancer might underestimate the incidence of TP53 mutations. When these mutated genes are compared to the wild type gene, e.g. the normal gene, not all mutations will lead to an abnormal protein and thus with interference of cell apoptosis. This method enables further research to analyze large numbers of patients with colon cancer for TP53 mutations in a reliable and concise way.

In chapter V and VI the relationship between TP53 and KRAS mutations on one hand and prognosis in adjuvantly treated Dukes’ C colon cancer patients on the other hand, is described. The KRAS gene is located on chromosome 12 and is a frequently mutated oncogene in colorectal cancer. The incidence of KRAS mutations is higher in polyps than in invasive cancer suggesting a role of KRAS mutations in the initiation of cancer, although some authors report an effect on phenotypic tumor behavior as well. The KRAS oncogene down regulates cell growth and cell differentiation by way of the adenylate cyclase, a transduction of external stimuli takes place and growth factors initiate cell differentiation. Point mutations in the KRAS gene lead to an altered p21 protein, which activates the cell to autonomous growth. TP53 and KRAS mutations are thought to be negative prognostic factors. Due to the many genes involved in the oncogenesis of colorectal cancer (DCC, APC, MMHc1 etc) these negative influences are difficult to analyze clinically. Because the combination of two prognostic variables may lead to a more aggressive tumoriological behavior it is hypothesized that a subgroup of patients with Dukes C colon cancer reacts differently on chemotherapy. In chapter V the clinical data of the first 55 patients who entered the IKN 90-11 colon trial were correlated with samples of the paraffin embedded tumors analyzed for TP53 and KRAS gene mutations. It was thought that patients with both mutations had shorter survival and higher recurrence incidences. In Chapter V analysis has been focused on the relationship between overall survival and KRAS and/or TP53 mutations. In this study, patients with KRAS and/or TP53 mutated Dukes’ C colon tumors had the same survival as non-mutated tumors. In a similar study of Finkelstein et al, explicit survival differences were found in an identical group of Dukes’C stage colon cancer patients. Compared to our results the only difference found was the current addition of adjuvant chemotherapy. It is therefore concluded. Although the literature suggest that KRAS and TP53 are prognostic indicators in colon cancer, current data suggest that if patients are treated with 5FU based chemotherapy K-RAS and TP53 cannot be used as prognostic indicators. The question remains whether this is coincidence or a chemotherapeutic effect. Further research is initiated to evaluate all patients who participated in the IKN 90-11 colon trial to confirm the results of the pilot study presented in chapter V.
In chapter VI the incidence of TP53 and KRAS mutations in left and right-sided Dukes C colon tumors is discussed. Clinical observations have suggested that right-sided colon tumors have a more aggressive tumorbiological behavior compared to left sided tumors. Furthermore the incidence of right-sided tumors is increased in the last 40 years. It is possible that intraluminal mutagenic factors differ in the right and left colon, which might influence mutations in onco- and suppressor genes. KRAS mutations are known to have a higher incidence in right-sided tumors suggesting that tumor biological behavior in the left colon is influenced by other mutations. In this study the incidence of KRAS mutations was higher in right-sided Dukes’ C colon tumors. KRAS mutated tumors in the left colon had a worse survival compared to right sided mutated tumors but due to the low incidence of KRAS mutations in the left colon differences between left and right-sided tumors could not be evaluated. In contrast to KRAS mutations, the incidence of TP53 mutations was equally divided between right and left sided colon tumors. TP53 mutations did not influence survival of left or right-sided colon tumors. Although differences in survival in left and right-sided Dukes’C colon cancer might be explained for the larger part by KRAS mutations, research on larger populations are necessary to elucidate the precise relationship between genetic mutations and tumor location. Future research on genetic differences between right and left-sided sporadic colon cancer should be focused on other genes also as for example mismatch repair genes.

In chapter VII the results of a prospective randomized Phase III trial comparing 5FU/Levamisole and Leucovorin/5FU/Levamisole in the adjuvant treatment of Dukes C colon cancer are discussed. In this study, performed in the northern and eastern part of the Netherlands with the cooperation of more than 40 hospitals, 500 patients were randomized. After a median follow-up of almost 4 years no differences in survival were noticed. However, toxicity increased substantially with the addition of leucovorin to the combination of 5FU and Levamisole. Therefore the addition of Leucovorin to 5FU and Levamisole is not advised in the adjuvant treatment of Dukes C colon cancer.

In Chapter VIII the follow-up of patients involved in the IKN 90-11 colontrial is described. Patients were evaluated regularly with colonoscopy, liver ultrasound and/or CT, CEA, physician visits and chest X-rays. By retrospective analysis, the first diagnostic modality identifying cancer recurrence is described. Liver ultrasound and colonoscopy identified almost 50% of patients suitable for salvage surgery. Twenty-seven percent of 42 patients
suitable for salvage surgery were identified after evaluation of symptoms. Only a minority of patients suitable for salvage surgery was identified by means of CEA, chest X-rays and routine physician examination. Concluded is that routine ultrasound and colonoscopy are useful in the follow-up of patients with adjuvantly treated Dukes C colon cancer in spite of current ASCO recommendations. On the other hand a substantial number of patients suitable for salvage surgery will also be identified after the evaluation of intercurrent symptoms. The gain of CEA, chest X-rays and routine physician visits is limited in identifying patients suitable for salvage surgery.