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ACCEPTED ABSTRACT

MSI CANCER: FROM GENOMICS TO PERSONALIZED MEDICINE

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The human tumor phenotype referred to as MSI (Microsatellite Instability) arises because of defects in the DNA mismatch repair (MMR) system. MSI was first observed in inherited tumors associated with Lynch syndrome and later in approximately 10-15% of sporadic colon, gastric and endometrial cancers, as well as in a small proportion (1-5%) of many other primary tumour types. The normal function of the MMR system is to recognize and repair the errors that arise during DNA replication, as well as to repair some forms of DNA damage. It is now well established that MMR deficiency is not in itself a direct transforming event and that MSI tumors develop through a distinctive molecular pathway characterized by the genetic instability of numerous microsatellite repeated sequences throughout the genome. These mutations accumulate in tumor cells together with other somatic alterations at non-repetitive DNA sequences. The overall aim of our research team is to decipher the important genomic and pathophysiological aspects of MSI carcinogenesis and to benefit from our findings to open perspectives for the precision medicine of MSI cancer. The overall aim of my talk will be to describe some important pathophysiological aspects of MSI carcinogenesis, reporting how the investigation of mechanisms underlying MSI-driven tumor development has also led us to identify diagnostic tools, risk factors, prognostic biomarkers, and new targets for personalized treatments of patients suffering from MSI tumors.



Note:

GAS CHROMATOGRAPHIC-MASS SPECTROMETRIC DETERMINATION OF ESTERS OF O-PHTHALIC ACID IN PHARMACEUTICAL ETHANOL COUPLED WITH EMULSION LIQUID-PHASE MICROEXTRACTION PRECONCENTRATION

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Dialkyl-o-phthalates are very dangerous compounds. In this study the high sensitive gas chromatographic-mass spectrometric determination of phthalates in ethanol coupled ultrasound-assisted emulsification-microextraction was developed. In the case of preconcentration of impurities from ethanol dilution was carried out with purified water. n-Octane, n-hexane and m-xylene were used as extractants. De-emulsification of extracts was carried out by centrifugation and flotation. The sources of possible systematic errors were investigated: leaking of o-phthalates from chromatographic septum; contamination of phthalates in solvents; influence of ethanol; the hydrolysis of o-phthalates and others. For the first time it is shown that the impact of these factors can lead to an overestimation or underestimation of the actual concentration of impurities by 1-2 orders of magnitude. The methods of accounting or elimination of systematic errors are proposed. Purification of solvents by Rayleigh distillation method allows to obtain samples with impurity content lower than $(1-4) \cdot 10^{-3}$ mgL⁻¹. Containers for sampling and storage of samples to be analyzed should be made of borosilicate glass or quartz. The limits of detection of esters of o-phthalic acid are at the level of 10-6-10-5 mgL⁻¹ and are highly competitive with the best world results. The content of o-phthalates in ethanol was 0.01-30 mgL⁻¹. The relative expanded uncertainty of the determination of toxicants is at the level of 13- 30%.



Note:

LONG-TERM OBSERVATION IN A LARGE GERMAN IBD REGISTRY

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Background: Inflammatory Bowel Disease (IBD) is diagnosed in approximately 350000 patients in Germany with increasing incidence and prevalence. Although on-going inflammation can result in irreversible damage to the GI tract, under-treatment and reluctance to use immunomodulatory therapies earlier in the course of disease are present. On the other hand, costs for therapies, surgeries and hospitalization are high, once damage has occurred. In 2015 we therefore implemented an independent national IBD registry (CEDUR) to methodically collect real life data of IBD patients with regard to the usefulness and comparability of immunomodulatory strategies.

Methods: CEDUR is a web-based, descriptive registry of large tertiary IBD centers throughout Germany, using time sparing documentation in an adapted medical charts-software via GDT interface. Patients with IBD who are willing to participate have visits every three months and fill in questionnaires that are later-on completed and controlled by their physicians. Since 2015 and for at least ten years, data on phenotypes, therapeutic effects including efficacy, safety and economy as well as hospitalizations, surgeries, comorbidities, day-off-work and quality of life are continuously collected in patients with Crohn's Disease (CD) and Ulcerative Colitis (UC).

Results: So far, 1856 IBD patients (UC: 859, CD: 992, indeterminate colitis 5) were enrolled, of whom 47% are men and 53% are women. In CD and UC, 24.3% were younger than 21 years, 38.6 between 21 and 30, 19.0% between 31 and 40, 10.5% between 41 and 50 and 7.5% older than 50 years. In CD, age at first diagnosis was younger than 21 in 29.8% and older than 50 years in 6.5%. In UC, age at first diagnosis was younger than 21 years in 17.6% and older than 50 years in 28.8%. In CD, biologics were used in 73.9% of patients, of those anti-integrins in 6.0% and IL-12/23 blockers in 5.6%. 31.4% of patients with TNF-blockers were treated for more than 4 years. 54.2 % of patients under infliximab received infusions every 7 to 9 weeks, 31.6% every 4 to 6 weeks. 49.5 % of patients under adalimumab received injections of 40mg every 2 weeks, and 38.4 % at least 80mg every 2 weeks. In UC, TNF-blockers or other biologics were used in 59.0% of patients, of those anti-integrins in 12.05% and IL-12/23 blockers in 0.2%. 24.8% of patients with TNF-blockers were treated longer than 4 years. 47.1 % of patients under infliximab received infusions every 7 to 9 weeks, 36.9% every 4 to 6 weeks. 52.7 % of patients under adalimumab received injections of 40mg every 2 weeks, and 37.9% at least 80mg every 2 weeks.

Conclusions: We successfully implemented a large national IBD registry for the collection of real life data by a contribution of patients and physicians from tertiary IBD centers throughout Germany. As a first result we can present the data on the use of biologic therapy in more than 1800 Crohn's disease and ulcerative colitis patients. IBD significantly affect patients in their young ages, biologic therapies seem to be necessary in much more patients than commonly assumed and standard treatment has to be adapted to higher doses in TNF-blockers in UC more than CD and in adalimumab more than infliximab. Our registry can serve as data base for a wide range of efficacy, safety and economy issues in IBD patients.