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Tumor diagnosis and DNA - microarrays

Abstract not received.

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Measuring the clinical response: What does it mean?

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In Oncology and more specifically in advanced or locally advanced diseases, patient's response to anticancer treatment has been and remains the first indicator of the possible benefit that patients and clinicians are looking for after the start of the treatment. The assumption that patients' response may be linked to a possible benefit for the patient is based on the fact that usually "responders do better" on the long term. How should this last sentence be interpreted?

The evaluation of the tumor response in day to day practice is usually based on the combined results provided by several examinations including the tumor burden (imaging techniques), tumor markers, and the clinical performance of the patient. The decision to continue or stop the treatment is made by the treating physician following its own judgement. What are the factors to be integrated to evaluate the clinical response in such a context?

The evaluation of the tumor response in clinical trials is often taken as an endpoint of the study on which the investigator has built his/her hypothesis. It is used as a primary endpoint of trials designed to screen new anticancer agents to detect and quantify their antitumor activity. In this context the evaluation of the tumor response follows very strict rules normally pre-defined in the protocol. What's the meaning of antitumor activity? What are the rules to measure such activity? How is this methodology evolving with new imaging techniques and new drugs with non-cytotoxic mechanisms of action?

Tumor response is also taken as a primary or secondary endpoint in trials aiming at the determination of the efficacy of new treatment or combination of treatments. In this setting tumor response is assimilated to a surrogate indicator of the clinical outcome being investigated. What are the characteristics of a true surrogate indicator? Does it apply to tumor response and under which circumstances? What are the rules to measure the efficacy? Are there valid alternatives?

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DNA instability and repair

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Mutations in tumor suppressor genes and oncogenes may trigger malignancy. These mutations often occur as consequences of exposure of DNA to environmental and endogenous damaging agents. A large proportion of cellular DNA damage is unavoidable since it is generated accidentally by spontaneous hydrolysis at 37oC, and by exposure to active oxygen and reactive metabolites and coenzymes. Consequently, it is an impossible task to try to prevent totally the occurrence of cancer in man. Most, but not all, DNA damage is removed by various DNA repair processes, including excision-repair and recombinational repair pathways. We have reconstituted human excision-repair processes for endogenous DNA damage with purified protein factors after cloning and overexpression. We have also constructed gene knockout mice lacking certain relevant repair enzymes, including the DNA ligase that joins DNA double-strand breaks, DNA glycosylases which excise the major mutagenic base derivatives generated by hydrolysis and by reactive oxygen species, and a nuclear 3' exonuclease involved in DNA editing. Unexpected phenotypes of the mutant mice have revealed complexity and diversification of DNA repair processes in mammalian cells.

References

[1] T. Lindahl and D.E. Barnes. Repair of endogenous DNA damage. Cold Spring Harbor Symp. Quant. Biol. 65, 127-133 (2000)

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Stomach cancer - an infectious disease ?

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Gastric cancer is the second most common fatal malignancy in the world and is the cause of around one million deaths annually. Most gastric cancer is diagnosed at an advanced stage and, outside Japan, survival is uniformly poor - usually no more than 15% at five years. There is now considerable epidemiological evidence supportive of an association between infection with a common bacterium, Helicobcater pylori, and an increased risk of gastric cancer. Most of the descriptive epidemiology of gastric cancer parallels that for H. pylori infection especially the strong association with poor socioeconomic conditions. The most persuasive evidence indicative of an association is that from prospective serological studies of gastric cancer. A recent meta-nalysis shows that these are now consistent in showing an approximate three to sixfold increased risk of non-cardia cancer in H. pylori positive individuals. This indicates that at least half of all non-cardia cancer can be attributable to the infection. Very few established causes of cancer have been associated with an attributable risk of this magnitude.

The critical question which follows concerns the extent to which H. pylori-induced precancerous changes will regress or be prevented from progression after eradication. H. pylori eradication therapy, using a relatively simple course of antibiotics, offers a one-off cost-effective means of reducing exposure to a major cause of cancer. The case for population based intervention, balancing out risks and benefits, still has to be made but control of H. pylori is likely easier to achieve than control of exposures requiring behavioural change (e.g. smoking, diet, sunlight). It will also be cheaper than other screening interventions requiring expensive technology and/or frequent repeats (e.g. mammography, cervical cytology). Evidence from controlled intervention studies is now beginning to accumulate.

Much remains to be established about the relationship, in particular the reason why certain populations or patient groups have relatively low gastric cancer rates despite high levels of infection and why the gastric cardia is apparently protected from the carcinogenic effects of H. pylori.