Contemporary Oncology Issues

Staying current with the literature has never been more challenging due to the sheer number of articles published. To help you stay abreast, we search leading oncology journals for topics with the broadest impact on patients with cancer and explore them, one topic at a time.

The content in this section is updated regularly, so be sure to check back often.

Personalised Medicine in Cancer Treatment

The National Cancer Institute of the United States defines personalised medicine as "*a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease.*"[1] Yet the practical path to this goal can be less than clear to clinicians caring for patients with cancer, who struggle with predicting which treatments will be effective for a specific patient.[2] Ideally, cancer treatment decisions will ultimately be based on a patient's clinical presentation combined with their molecular profile and other individual characteristics, rather than on uniform protocols derived from average treatment responses of broad groups of patients.[2]

This commentary on personalised medicine provides a simplified overview of this contemporary issue and its evolving role in cancer treatment.

Setting the stage for individualised therapy

The past two decades have revealed new details on the basic biological processes contributing to cancer development including growth factor binding, signal transduction, epigenetics, gene transcription and control, cell cycle checkpoints, apoptosis, and tumour angiogenesis.[3,4] These basic science advances set the stage for individualising cancer treatment.

Cancers arise from a variety of causes and each individual with cancer represents a unique pathogenesis, pattern of tumour invasion, and aggressiveness. Such biologic variations exist even among individuals with the same tumour type, and underlie the differences in how patients respond to particular cancer therapies.[5,6] Using these variations to select the right drug for the right patient, or rational pharmacotherapy, is at the heart of personalised medicine.[3,7,8]

Personalised medicine represents the progression of medical science away from generalised treatment decisions towards individualised treatment courses. However, personalised medicine is not one clinical technique—it is a set of practices incorporating screening, risk assessment, diagnosis, and prognosis, as well as predicting treatment responses, adjusting doses based on pharmacogenomics, detecting early recurrence, and stratifying patients into cancer subtypes.[6,9]

The inherent variability among individuals with cancer drives personalised medicine in this setting.[6] Today's oncology clinical practitioners are at the forefront of the practical application of personalised medicine strategies. The diagnosis of cancer relies heavily on biopsy and examination of the tumour; advances in immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and chromogenic in situ hybridization (CISH) have paved the way for pharmacodiagnostic testing to detect overexpression of

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tumour proteins and genetic aberrations.[8]

Personalised medicine in patients with cancer

Stepwise advances are integrating personalised medicine into cancer treatment, with therapies evolving from nonspecific cytotoxic drugs to more targeted approaches using the molecular signature of a patient's disease to guide treatment. The first important step is the division of patients into biological subgroups that present different risks or respond differently to therapy.[10] As the understanding of tumour pathophysiology at the molecular level grows, these subgroups become increasingly smaller. Subsequently, clinical decisions can be refined for these subgroups.

Although fully individualised drug therapy has not yet been realised, oncologists may apply several principles of personalised medicine to clinical practice.

Screening, tumour classification, and prognosis

Identifying biologic subgroups of patients currently assists clinicians in screening patients for risk of developing certain cancers, classifying and subtyping tumours, and defining a given patient's prognosis.[6]

Approximately 100 genes are associated with a risk of developing a variety of cancers.[3] Screening for mutations in genes such as BRCA1 and BRCA2, the DNA mismatch repair genes MLH1 and MSH2, and RET provides patients with information about their risk of developing breast, ovarian, colon, and endocrine neoplasia respectively.[11-14] Knowledge of a predisposition for a specific type of cancer can lead to increased surveillance and vigilance, resulting in earlier detection and intervention.

Diagnostic biomarkers such as gene expression assays also refine risk stratification based on the underlying tumour biology.[7] Molecular analysis has identified novel subgroups with unique prognostic outcomes for patients with acute myeloid leukaemia,[15,16] glioblastoma,[17] breast cancer,[18,19] renal cell carcinoma,[20] and to differentiate between Burkitt's lymphoma and diffuse B-cell lymphoma.[21] This distinctive prognostic information can then be applied to treatment decisions by identifying those requiring aggressive treatment, as well as those who can be spared more toxic therapies.[7]

Pairing subgroups with treatments

Genetic variations can be used to stratify treatments by predicting treatment efficacy as well as by predicting optimal treatment dose and safety in cancer patient subgroups.[2,10] Pharmacodiagnostic tests define these subgroups.

Specific molecular alterations predict the likelihood of a patient responding to several available cancer treatments. For example, the presence of the BCR-ABL-positive tyrosine kinase genotype, overexpression of the HER-2 receptor, mutations in the kinase domain of the epidermal growth factor receptor, downstream mutations of KRAS, and genetic variation in CYP2D6 can be used to predict response to therapies commonly employed in chronic myeloid leukaemia, breast cancer, non–small cell lung cancer, and other tumour sites.[22-27]

Future perspectives on the personalised medicine path

Clearly personalised medicine will play an important role in future cancer treatment, and is already becoming a key part of selected cancer management plans. As well as helping predict which family members may be at risk of developing malignancy, molecular analysis may assist with treatment decisions throughout the course of a patient's cancer. For example, molecular subclassification during diagnosis, pharmacogenetics predicting treatment efficacy or resistance, as well as molecular early detection of recurrence or metastasis may all play a role in determining the optimal care for an individual patient.[2]

An important aspect of the future of personalised medicine is not only the development of precisely targeted drugs, but also the parallel development of pharmacodiagnostic tests for these drugs.[28,29] Biomarker development and drug and biomarker co-development present new challenges for clinical investigators, regulators, and the pharmaceutical and assay industries.[30] Important issues remain to be explored, including determining the role of biomarkers in drug development and whether to use biomarkers to establish patient eligibility for clinical trials; defining regulatory pathways to coordinate approval of co-developed diagnostics and therapeutics; and identifying methods to accurately assess the validity and clinical utility of diagnostics.[7,30,31]

Over the coming years, personalised medicine will continue to evolve, as researchers explore newly discovered genes, proteins, and pathways.

Further Reading

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Hamburg MA, Collins FS. The path to personalized medicine. New Engl J Med. 2011;363(4):301-304.

Sikora K. Personalized medicine for cancer: from molecular signature to therapeutic choice. Adv Cancer Res. 2007;96:345-369.

Instant Survey

Which one of the following contemporary issues in oncology would you most like to see covered?

Take the Survey

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What texts and journal articles remain invaluable to each new generation of oncologists? What keeps them relevant year after year? Add our suggestions—updated regularly—to your reading list. And be sure to share your opinion (and view those of your peers) via our interactive survey.

Publications of major advancements

This collection focuses on publications representing significant advances in cancer biology and changing clinical practices. These are selected publications that can be considered classic reading in oncology. This seminal reading collection is obviously not all-encompassing yet provides timeless perspectives and thought-provoking reading.

Linking smoking and lung cancer

Doll R, Hill AB. Smoking and carcinoma of the lung: preliminary report. *British Medical Journal*. 1950;2(4682):739-748.

During the first half of the 20th century, smoking was not considered a public health problem, and the hazards of smoking had not been established.[1] However this changed in 1950, when Drs. Doll and Hill published this landmark paper linking smoking and lung cancer.[2]

This case-controlled study implicated the use of tobacco as a major risk factor for the disease.[2] In addition, this preliminary analysis also clearly showed that the risk of developing lung cancer increased steadily as the amount of smoking increased. Although controversial at the time of original publication, these results were confirmed by further research including prospective evaluations over the past 50 years, as summarized in a 2004 publication by Doll et al.[1]

Also see: Doll R, Peto R,Boreland J, Sutherland I, Mortality in relation to smoking: 50 years' observations on male British doctors. *British Medical Journal*. 2004; 328:1519-1527.

Illuminating the natural history of carcinoid tumours by considering "the land of small tumours"

Moertel CG. Treatment of the carcinoid tumour and the malignant carcinoid syndrome. *Journal of Clinical Oncology*. 1983;1(11):727-740.

This classic paper published in 1983 as part of the first year of the *Journal of Clinical Oncology*,[3] along with Dr. Moertel's subsequent 1987 Karnofsky Memorial lecture,[4] provides timeless insights into the natural history and clinical behaviour of carcinoid and gastrointestinal neuroendocrine tumours.

Dr. Moertel discusses clinical pearls such as the link between stage of disease and tumour aggressiveness, the potential to target unique tumour metabolic characteristics with more sophisticated

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therapies, and the opportunity to focus experimental therapies on fundamental physiologic features.[3] A central message of this seminal publication is that research focusing an "experienced, multidisciplinary clinical team supported by devoted basic scientists" is a potential route to more curative therapy.

Also see: Moertel CG. An odyssey in the land of small tumours. *Journal of Clinical Oncology*. 1987;5(10):1503-1522.

Aligning treatment response definitions

Therasse P, Arbuck AG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumours. *Journal of the National Cancer Institute*. 2000;92(3):205-216.

Assessing changes in tumour burden is central to the clinical evaluation of cancer therapeutics. In addition to overall survival, both tumour shrinkage (objective response) and time to the development of disease progression are important endpoints in cancer clinical trials. Over time, inconsistencies in defining these endpoints evolved to the point where response data was no longer comparable across different research groups.[5] In 2000, the Response Evaluation Criteria in Solid Tumours (RECIST 1.0) was first published, [5] setting forth rules defining when cancer patients improve (respond), worsen (progression) or stay the same (stable) during treatment.

The RECIST guidelines are now employed in the majority of clinical trials around the world evaluating cancer treatments for objective response or progression free survival. These well-accepted global response criteria were revised in 2009 to better reflect the realities of clinical practice, the growing importance of disease progression as a primary endpoint, and the evaluation of non-cytotoxic therapies.[6]

Also see: Eisenhaur EA, Therasse P, Bogaerts L, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European Journal of Cancer*. 2009;45:228-247.

Exploring the cancer genome

Stratton MR, Campbell PJ, Futreal PA. The cancer genome. *Nature*. 2009;458:719-724.

This review article summarises the current knowledge on how changes in the DNA sequence of the genomes of cancer cells lead to cancer development. The authors note that while approximately 100,000 somatic mutations from cancer genomes have been reported since the first was found in the HRAS gene, several hundred million more are expected to be revealed by large-scale complete cancer genome sequencing projects.[7]

This expanding information on the cancer genome should further illuminate the processes underlying cancer development, potentially guiding new treatment strategies.

Considering a pleuripotent cancer stem cell

Quintana E, et al. Efficient tumour formation by single human melanoma cells. *Nature*.2008;456:593-598.

This important study from the active field of cancer stem cell research provides convincing evidence that the cancer stem cell frequency in melanoma is approximately 25%.[8] This suggests that a significant proportion of cells constituting therapeutic targets may be programmed to become cancer cells. Publications such as this one are valuable resources as researchers pursue the goal of personalised medicine. Gaining new details and more comprehensive information on how cancers develop may illuminate additional targets for novel therapeutics.

Instant Survey

Which of the following areas do you believe would yield the most useful seminal publications for oncology reading?

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