special symposium: germline genetics: important issues for oncologists

CONSIDERATIONS FOR THE ONCOLOGIST WHEN TREATING CANCER PATIENTS WITH GERMLINE MUTATIONS

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Cancer therapy is now entering the arena of personalised medicine with therapies targeted to specific tumour or host features. Much of the focus to date has been on somatic genetic changes, such as KRAS mutations in colorectal cancer and BRAF mutations in melanoma, to select for subgroups of patients with the optimal tumour genetic profile for response to targeted therapies. However, the germline genetic profile of patients can also have a major impact on the outcome of cancer therapy by affecting either the chance of response and/or the chance of side effects from treatment.

Germline mutations are present in every tumour cell, unlike the genetic heterogeneity of sporadic tumours which are unlikely to have the same crucial mutation in every tumour cell (chronic myeloid leukaemia and gastro-intestinal stromal tumours being notable exceptions), so theoretically increasing the chance of response to a mutation-targeted agent. Examples of germline genetic-driven therapy include the extent of breast cancer surgery at the diagnosis of early breast cancer, the use of poly (ADP-ribose) polymerase inhibitors in BRCA-driven cancers, the use of adjuvant chemotherapy in mismatch repair-deficient colorectal cancer, choice of treatment in early BRCA-driven prostate cancer and the role of smoothened inhibitors in PTCH-associated basal cell carcinomas. In contrast, knowledge of germline genetics can indicate what treatments to avoid where possible, without compromising the chance of cure, such as radiotherapy in people with TP53 or PTCH mutations causing the Li Fraumeni and Gorlin syndromes respectively. Using germline genetics to guide cancer therapy has been limited by the expense, timeliness (or not) of testing and the general appetite (or not) for testing by patients, the medical community and society as a whole. Times are changing; testing is becoming cheaper, faster and society is gradually appreciating the power of genetic information providing safeguards to its use are in place. The challenge is how to integrate germline assessments into routine cancer care across different oncology environments in order to maximise the therapeutic potential of this information.

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