Genetics

Pathogenic ATM Mutations in Cancer and a Genetic Basis for Radiotherapeutic Efficacy

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BACKGROUND

Radiation therapy is one of the most commonly used cancer therapeutics, but genetic determinants of clinical benefit are poorly characterised. Pathogenic germline variants in the ataxia telangiectasia mutated (ATM) gene are known to cause ataxia-telangiectasia, a rare hereditary syndrome notable for marked radiosensitivity. In contrast, somatic inactivation of ATM is a common event in a wide variety of cancers, but its clinical actionability remains obscure.

METHODS

We analysed 20107 consecutively treated advanced cancer patients who underwent targeted genomic sequencing as part of an institutional genomic profiling initiative and identified 1085 harbouring a somatic or germline ATM mutation, including 357 who received radiotherapy. Outcomes of irradiated tumours harbouring ATM loss-of-function (LoF) mutations were compared to those harbouring variants of unknown significance (VUS). All statistical tests were two-sided.

RESULTS

Among 357 pan-cancer patients who received 727 courses of radiotherapy, genetic inactivation of ATM was associated with improved radiotherapeutic efficacy. The two-year cumulative incidence of irradiated tumour progression was 13.2% vs. 27.5% for tumours harbouring an ATM LoF vs. VUS allele, respectively (hazard ratio (HR): 0.51, 95% CI = 0.34-0.77, p= 0.001). The greatest clinical benefit was seen in tumours harbouring bi-allelic ATM inactivation (HR = 0.19, 95% CI = 0.06-0.60, p=0.005), with statistically significant benefit also observed in tumours with mono-allelic ATM inactivation (HR = 0.57, 95% CI = 0.35-0.92, p=0.02). Notably, ATM LoF was highly predictive of outcome in TP53 wild-type tumours, but not among TP53-mutant tumours.

CONCLUSION

We demonstrate that somatic ATM inactivation is associated with markedly improved tumour control following radiotherapy. The identification of a radiosensitive tumour phenotype across multiple cancer types offers potential clinical opportunities for genomically-guided radiotherapy.