an overall increase in survival in the absence of overt toxicity or severe hematopoietic side effects. Overall, these results provide strong evidence that small molecule inhibition of DOT1L represents a potential targeted therapeutic against MLL-translocated leukemia, a disease that currently has limited treatment options.


Radiotherapy

**Major finding:** Intermediate-risk group of patients with localized prostate cancer benefit from combined radiotherapy and short-term ADT.

**Clinical outcome:** Combined radiotherapy with ADT resulted in 10-year overall survival of 62%.

**Future direction:** Optimal radiation dose for these patients must be determined and longer follow-up may be required to observe benefits in patients with low-risk disease.

**COMBINED RADIOTHERAPY AND ANDROGEN-DEPRIVATION THERAPY**

External beam radiation therapy plus androgen-deprivation therapy (ADT) is standard of care for men with advanced localized adenocarcinoma of the prostate, and it has been suspected but not known whether this combined therapy would be effective among patients with early localized disease. Jones and colleagues report on a phase III study of 1,979 patients with early-stage prostate adenocarcinoma treated either with radiotherapy alone or radiotherapy plus ADT with a mean follow-up of 9.1 years. The addition of ADT was associated with an improvement in the primary endpoint, 10-year overall survival, from 57% to 62%. Secondary endpoints including disease-specific mortality, distant metastases, increasing prostate-specific antigen levels, and positive findings on repeat biopsies were also significantly improved. Risk analysis showed that improvements in overall survival and disease-specific mortality were seen primarily among intermediate-risk patients, with no significant reductions among low-risk patients.


Genomics

**Major finding:** Study reports on messenger RNA and microRNA expression, promoter methylation, and DNA copy number in high-grade serous ovarian adenocarcinomas.

**Impact:** Up to half of these cancers may have aberrations in genes involved in homologous recombination and thus benefit from PARP inhibitors.

**Approach:** Large-scale analysis of genomic aberrations identifies many genes as potential therapeutic targets.

**INTEGRATED GENOMIC ANALYSIS OF OVARIAN CARCINOMA**

Identification of disease-associated molecular alterations is critical for the development of targeted therapeutics. The Cancer Genome Atlas Research Network has reported on a large-scale analysis of messenger RNA and microRNA expression, promoter methylation, and DNA copy number in 489 high-grade serous ovarian adenocarcinomas. Nearly all high-grade serous ovarian carcinomas were found to have mutations in p53 as well as several genes mutated at lower frequencies, including CDK12, a kinase involved in regulation of RNA splicing. Gene expression analysis identified 4 distinct subtypes of ovarian cancer. Pathway analyses suggest that homologous recombination is defective in about half of the tumors analyzed, and that NOTCH and FOXM1 signaling are involved in serous ovarian cancer pathophysiology. Additionally, 22 genes for which inhibitors already exist were identified in regions of recurrent amplification.

Combined Radiotherapy and Androgen-deprivation Therapy

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