RESEARCH

Chemotherapy weakly contributes to predicted neoantigen expression in ovarian cancer

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Abstract

Background: Patients with highly mutated tumors, such as melanoma or smoking-related lung cancer, have higher rates of response to immune checkpoint blockade therapy, perhaps due to increased neoantigen expression. Many chemotherapies including platinum compounds are known to be mutagenic, but the impact of standard treatment protocols on mutational burden and resulting neoantigen expression in most human cancers is unknown.

Methods: We sought to quantify the effect of chemotherapy treatment on computationally predicted neoantigen expression for 12 high grade serous ovarian carcinoma (HGSC) patients with pre- and post-chemotherapy samples collected in the Australian Ovarian Cancer Study. We additionally analyzed 16 patients from the cohort with post-treatment samples only, including five primary surgical samples exposed to neoadjuvant chemotherapy. Our approach integrates tumor whole genome and RNA sequencing with class I MHC binding prediction and mutational signatures of chemotherapy exposure extracted from two preclinical studies.

Results: The mutational signatures for cisplatin and cyclophosphamide identified in a preclinical model had significant but inexact associations with the relevant exposure in the clinical samples. In an analysis stratified by tissue type (solid tumor or ascites), relapse samples collected after chemotherapy harbored a median of 90% more expressed neoantigens than untreated primary samples, a figure that combines the effects of chemotherapy and other mutagenic processes operative during relapse. Neoadjuvant-treated primary samples showed no detectable increase over untreated samples. The contribution from chemotherapy-associated signatures was small, accounting for a mean of 5% (range 0–16) of the expressed neoantigen burden in relapse samples. In both treated and untreated samples, most neoantigens were attributed to COSMIC *Signature (3)*, associated with BRCA disruption, *Signature (1)*, associated with a slow mutagenic process active in healthy tissue, and *Signature (8)*, of unknown etiology.

Conclusion: Relapsed HGSC tumors harbor nearly double the predicted expressed neoantigen burden of primary samples, but mutations associated with chemotherapy signatures account for only a small part of this increase. The mutagenic processes responsible for most neoantigens are similar between primary and relapse samples. Our analyses are based on mutations detectable from whole genome sequencing of bulk samples and do not account for neoantigens present in small populations of cells.

Keywords: neoantigen; mutational signature; chemotherapy

Background

Many chemotherapies including platinum compounds [1], cyclophosphamide [2], and etoposide [3] exert their effect through DNA damage, and recent studies have found evidence for chemotherapy-induced mutations in post-treatment acute myeloid leukaemia [4], glioma [5], and esophageal adenocarcinoma [6]. Successful development of immune checkpoint-mediated therapy[7] has focused attention on the importance of T cell responses to somatic mutations in coding genes that generate neoantigens [8]. Studies based on bulk-sequencing of tumor samples followed by computational peptide-class I MHC affinity prediction [9] have suggested that tumors with more mutations and predicted mutant MHC I peptide ligands are more likely to respond to checkpoint blockade immunotherapy [10, 11]. Ovarian cancers fall into an intermediate group of solid tumors in terms of mutational load present in pre-treatment surgical samples[12]. However, the effect of standard chemotherapy regimes on tumor mutation burden and resulting neoantigen expression in ovarian cancer is poorly understood.

Investigators associated with the Australian Ovarian Cancer Study (AOCS) performed whole genome and RNA sequencing of 79 pre-treatment and 35 post-treatment cancer samples from 92 HGSC patients, including 12 patients with both pre- and post-treatment samples [13]. The samples were obtained from solid tissue resections, autopsies, and ascites drained to relieve abdominal distension. Treatment regimes varied but primary treatment always included platinum-based chemotherapy. In their analysis, Patch et al. reported that post-treatment samples harbored more somatic mutations than pre-treatment samples and exhibited evidence of chemotherapy-associated mutations. Here we extend these results by quantifying the mutations and predicted neoantigens attributable to chemotherapy-associated mutational signatures. We find that, while neoantigen expression increases after treatment and relapse, only a small part of the increase is due to mutations associated with chemotherapy signatures.

Content

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Sub-sub-sub heading for section Text for this sub-sub-sub-heading ... In this section we examine the growth rate of the mean of Z_0, Z_1 and Z_2. In addition, we examine a common modeling assumption and note the importance of considering

the tails of the extinction time T_x in studies of escape dynamics. We will first consider the expected resistant population at vT_x for some $v > 0$, (and temporarily assume $\alpha = 0$)

$$E\big[Z_1(vT_x)\big] = E\bigg[\mu T_x \int_0^{v\wedge 1} Z_0(uT_x)\exp\big(\lambda_1 T_x(v-u)\big)\,du\bigg].$$

If we assume that sensitive cells follow a deterministic decay $Z_0(t) = xe^{\lambda_0 t}$ and approximate their extinction time as $T_x \approx -\frac{1}{\lambda_0}\log x$, then we can heuristically estimate the expected value as

$$\begin{aligned} E\big[Z_1(vT_x)\big] &= \frac{\mu}{r}\log x \int_0^{v\wedge 1} x^{1-u}x^{(\lambda_1/r)(v-u)}\,du \\ &= \frac{\mu}{r}x^{1-\lambda_1/\lambda_0 v}\log x \int_0^{v\wedge 1} x^{-u(1+\lambda_1/r)}\,du \\ &= \frac{\mu}{\lambda_1-\lambda_0}x^{1+\lambda_1/rv}\left(1-\exp\left[-(v\wedge 1)\left(1+\frac{\lambda_1}{r}\right)\log x\right]\right). \quad (1) \end{aligned}$$

Thus we observe that this expected value is finite for all $v > 0$ (also see [14, **?**, **?**, **?**, **?**]).

Competing interests
The authors declare that they have no competing interests.

Author's contributions
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Figures

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