Functional and molecular characteristics of 20 novel patient-derived xenografts of Asian gastric cancer


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Introduction

In East Asia, stomach cancer is the 2nd most common malignancy and there is a high medical need to develop new drugs. However, well characterized in vitro and in vivo models developed from Asian cancer patients are rare. The Oncotest tumor xenograft and cell line repository used for profiling of anticancer compounds comprises mainly models established from Caucasian patients’ samples. Recently, the Oncotest tumor repository was extended by 20 gastric cancer xenografts of Asian origin from patients of the Seoul National University, South Korea. The aim of this study was to investigate the tumor biology and the response to chemotherapy of Asian gastric cancers.

Materials and Methods

In vivo efficacy tests:
- Tumors were grown subcutaneously in nude mice and treated with:
  - Paclitaxel 15 mg/kg/day on days 0, 7, 14
  - Cisplatin 6.4 mg/kg/day on days 0, 14
  - 5-FU 75 mg/kg/day on days 0, 7, 14

Mutational analyses:
- Sequences Focal 1, 2 and 3
- Mutations verified by Sanger Sequencing of exons and PTEN complete coding sequence

Results – histology

Figure 1. An example of the stability of histology from the patient tumor to the xenograft (GXA 3023)

The histology of the patient tumor is closely resembled by the xenograft in passage 7, mainly forming tubular glands.

Results – in vivo efficacy

Figure 2. In vivo efficacy of the standard of care compounds Paclitaxel, Cisplatin and 5-FU in two examples of gastric cancer xenografts derived from Asian patients.

Results – mutational analyses

Figure 4. Mutational analysis by gene.

- Individual tumors are represented by different colours.
- TP53, PTEN, PIK3CA, KRAS and MLH1 were frequently mutated.

Figure 5. Mutational analysis by tumor.

- Individual tumors varied in the mutation count and the combination of mutations.

Conclusions

These results demonstrate (i) that standard of care therapies are not effective in a large proportion of gastric cancers and (ii) great heterogeneity within the 18 analyzed gastric Asian patient-derived xenografts. Comparisons of genotype to phenotype, particularly including sensitivity to novel therapies, can be pursued using these models.

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• TP53, PTEN alteration rate of 49%/9/20
• PIK3CA, KRAS, MLH1 and especially TP53 were commonly mutated
• Mutation counts in individual gastric xenografts ranged from no to four mutations
• 14 different combinations of the analyzed mutations were found
• All MLH1-mutated tumors were resistant to the three standard of care chemotherapeutics.


Remissions were a rare occurrence.

61 % of tumors showed progressive growth with each of the three chemotherapies. Response to chemotherapy was independent of the growth rate of the tumor.

In the next section, figure shows high HER2 (ErbB2) expressing gastric cancer xenografts (*), for which treatment targeting HER2 may be more effective than standard chemotherapy. (see pooter p 2774)

Results – mutational analyses

Figure 3. Immunohistochemistry of HER2 vs control antibody shows GXA 3054, 3038, 3039 and 3067 are HER2 positive *