The status of Her2 amplification and Kras mutations in mucinous ovarian carcinoma

Kuang-Leei Chang¹, Ming-Yung Lee², Wan-Ru Chao³* and Chih-Ping Han⁴*

Abstract

Jayson GC et al. remarked in Lancet that nearly 100% of mucinous ovarian cancer cases have Kras mutation as well as a high frequency of Her2 amplification. Using the Abbott PathVysion Her2 DNA Probe Kit and Kras mutant-enriched PCR Kits (FemtoPath*), 21 samples of primary ovarian mucinous cystadenocarcinomas from Taiwanese patients were examined to determine the status of Her2 amplification and Kras mutations. Our results showed the Her2 amplification rates were 33.33%, while the Kras mutation rates were 61.90%. We present here our results in order to enlighten the readership that the ~100% Kras mutant frequency and the high Her2 amplification rate reported by Jayson et al. may be too exaggerated to be applicable into all populations. Additionally, we report another 2 novel Kras mutations (A11V, V14I).

Keywords: Kras mutation, Her2 amplification, Mucinous ovarian carcinoma

Main text

We read with great interest the work by Jayson et al. in Lancet (Oct. 2014). The authors presented a comprehensive review of outstanding quality. They remarked that mucinous ovarian carcinoma has a nearly 100% human V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (Kras) mutation as well as a high frequency of human epidermal growth factor receptor 2 (Her2) amplification [1]. However, we respectfully disagree with Jayson et al.’s opinion.

Literature reviews revealed that in mucinous ovarian carcinoma, the frequency of Her2 amplification/over-expression is estimated to be between 18 and 35% [2], and the presence of human Kras mutations is 13 to 60% [3–5]. This preliminary report aims to enlighten the readership that the ~100% Kras mutant frequency and the high Her2 amplification rate in mucinous ovarian carcinoma may be higher than what has been observed in other studies, including our own.

Briefly, genomic DNA was extracted from formalin-fixed, paraffin-embedded tissue blocks of 21 cases of mucinous ovarian carcinoma. All the donors’ identities have been permanently deleted. Abbott PathVysion Her2 DNA Probe Kit and the 2013 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) breast cancer scoring methods were used to examine for Her2 FISH ratio. The Kras mutant-enriched polymerase chain reaction (PCR) Kits (FemtoPath*) and a following direct sequencing method were applied to analyze exon 2 of the Kras gene. The reason why we choose Kras exon 2 to analyze is because Kras gene mutations are mainly known to cluster in several hotspots, with exon 2 (codons 12 and 13) being most commonly affected [6–9].

The prevalence of Kras mutations and Her2 amplification within 21 Taiwanese mucinous ovarian carcinoma cases is shown in Table 1, which indicates that the amplification rate of Her2 was 33.33% (n=7), while the mutation rate of Kras was 61.90% (n=13). Additionally, the rates of co-existing Kras mutations and Her2 amplification were 9.52% (n=2) (Table 1). However, there was a lack of statistically significant association between Her2 amplification and Kras mutations (p=0.057).

Of the 13 cases of mucinous ovarian carcinoma with Kras mutations, 12 cases had a single missense mutation, which was composed of G12V in 4 cases, G12D in 5 cases, G12A in 1 case and A11V in 2 cases. The remaining 1 case had triple missense mutations—A11V, G13N and V14I. Moreover, both A11V and V14I were novel discoveries, based on the Catalogue of Somatic Mutations in Cancer (COSMIC) database [10].

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and molecular modeling are encouraged. Still unknown; further studies using bioinformatics tools pacts of these 2 novel Kras with nonselective treatments. Additionally, functional im-
possibly produce superior therapeutic effects compared the protection of human subjects for research, including review and approval by the
Institutional Review Board of the Chung-Shan Medical University Hospital, Taichung, Taiwan.

Author details
1Department of Emergency Medicine, Chung-Shan Medical University and
Chung Shan Medical University Hospital, Taichung, Taiwan. 2Department of Statistics and Informatics Science, Providence University, Taichung, Taiwan.
3Department of Pathology, Chung-Shan Medical University and Chung Shan Medical University Hospital, Taichung, Taiwan. 4Department of Obstetrics and
Gynecology, Chung-Shan Medical University and Chung-Shan Medical University Hospital, No 110, Sec 1, Chien Kuo N. Rd, Taichung 40201, Taiwan.

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Table 1 The prevalence and relationship of Kras mutations and Her2 amplification in mucinous ovarian carcinoma

|                  | Her2 non-amplification | Her2 amplification | Total |
|------------------|------------------------|--------------------|-------|
| n (%)            | n (%)                  |                   | n (%) |
| Kras wild type   | 3 (14.29)              | 7 (33.33)          | 21 (100.00) |
| Kras mutation    | 11 (52.38)             | 2 (9.52)           | 13 (61.90) |
| P value          | 0.056*                 |                   |       |

n (%) number (percentage)
*Fisher’s exact test

Conclusion
Both Her2 amplification and Kras activating mutations are not mutually exclusive, which indicates that Her2/Kras/ mitogen-activated protein kinases (MAPK) is a crucial pathway in the carcinogenesis of mucinous ovarian neo-
plasms. Targeting this pathway seems to be a viable therapeu
tic option for patients with recurrent or advanced stage mucinous ovarian carcinoma. Treatment selection based on the molecular alterations of Her2 and Kras can possibly produce superior therapeutic effects compared with nonselective treatments. Additionally, functional im-
pacts of these 2 novel Kras mutations (A11V, V14I) are still unknown; further studies using bioinformatics tools and molecular modeling are encouraged.

Abbreviations
ASCO/CAP: American Society of Clinical Oncology/College of American Pathologists; COSMIC: Catalogue of Somatic Mutations in Cancer; Her2: Human epidermal growth factor receptor 2 gene; ICH: International Conference on Harmonization; Kras: V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog gene; MAPK: Mitogen-activated protein kinases; PCR: Polymerase chain reaction

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Availability of data and materials
Please contact the author for data requests.

Authors’ contributions
KLC and CPH provided the specimens and wrote the manuscript. MYL analyzed the data. WRC performed the experiments. All authors read and approved the final manuscript.

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

Consent for publication
Not applicable.

Ethics approval and consent to participate
Our research was conducted in accordance with the International Conference on Harmonization (ICH) guidelines and compliant with all applicable regulations for

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