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Short communication

Temporal offset association between the number of irinotecan-related adverse reactions and pharmacogenomic studies: A cross-correlation analysis

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ABSTRACT

Objectives: Studies have proved that UGT1A1 (*6, *28 and *93) gene polymorphism was closely related to the side effects of irinotecan. This study intends to perform a correlation analysis on the relationship between pharmacogenomic studies and ADRs based on time series.
Methods: The ADRs related to irinotecan were derived through the FAERS; searched all pharmacogenomic studies in PubMed and Web of Science; then analyzed the sequence of correlation coefficients between total ADRs, fatal ADRs and pharmacogenomic studies under different time offset.
Results: There is a positive correlation between the number of total ADRs and pharmacogenomic studies, of which the maximum correlation coefficient was 0.78 (95 % CI: 0.58–0.90), with a lag of 1 year. There is also a positive correlation between the number of fatal ADRs and pharmacogenomic studies, with the maximum correlation coefficient of 0.87 (95 % CI: 0.73–0.94) and a offset of − 4 years.
Conclusion: It was found that both the total ADRs and fatal ADRs were significantly positively correlated with change trend of published pharmacogenomic literatures, which confirmed the role of pharmacogenomic research in promoting the safe use of irinotecan, and have a faster response time in reducing fatal ADRs during clinical application.

1. Introduction

Irinotecan is an essential component of first and second line treatment chemotherapy regimens for advanced colorectal cancer, such as FOLFIRI, CapIRI, FOLFOXIRI and monotherapy (Benson et al 2021). It can also be used for gastric cancer, esophageal cancer and lung cancer, etc (Ajani et al 2022, Ettinger et al 2022). However, diarrhea and severe neutropenia are common adverse drug reactions (ADRs), which compromises the treatment outcomes by significantly impacting patient compliance and causing delay in chemotherapy cycles, and even lead to death (de Man et al 2018). Numerous studies have proven that UDP-glucuronosyltransferase 1A1 (UGT1A1, *6, *28 and *93) gene polymorphism was closely related to the occurrence of irinotecan side effects, adjusting its dose under the guidance of UGT1A1 genotype can greatly reduce the incidence and severity of adverse reactions, showed economic advantages and consequently save cost on healthcare systems. (Argevani et al 2020, Carrato 2022, Hulshof et al 2022, Kong et al 2022).

Irinotecan was first approved by the FDA in 1994 for the treatment of advanced colorectal cancer, but the association between its ADRs and UGT1A1 gene polymorphism was unknown until 1998 where this association was reported (Ando et al 1998). Nowadays, with the advancements in personalized medicine and the increase in its applicability, there are more published studies related to pharmacogenomics, including mechanism studies, case reports, clinical trials, and reviews. However, the data assessing the impact of pharmacogenomics on overall treatment safety in clinical practice are lacking.

The aim of this study is to perform a correlation analysis on the relationship between the timing of ADRs reporting and pharma-

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cogenomic studies publication and to highlight the lag time from basic research to clinical research, and eventually, to clinical application. In the correlation analysis, considering the lag from basic / clinical research to clinical application, a time-delay model is introduced (Muthuchellappan et al 2018, Shao et al 2022).

2. Methodology

2.1. Adverse drug reactions data collection

From January 1994 to December 2021, the ADRs related to irinotecan were derived through the adverse event reporting system of Food and Drug Administration (FAERS), with a total of 29, 994 cases by using the search term of irinotecan and irinotecan hydrochloride. After removing incomplete information such as age, sex, purpose, event date and those from non-health professionals (it is considered that the authenticity and accuracy of these cases were questionable), 13, 428 cases were retained for analysis (Fig. 1).

2.2. Pharmacogenomic studies collection

Taking irinotecan and UGT1A1 as terms in the abstract, we searched all literatures in PubMed and Web of Science. After removing the duplicate results, a total of 582 literatures were included in the follow-up analysis.

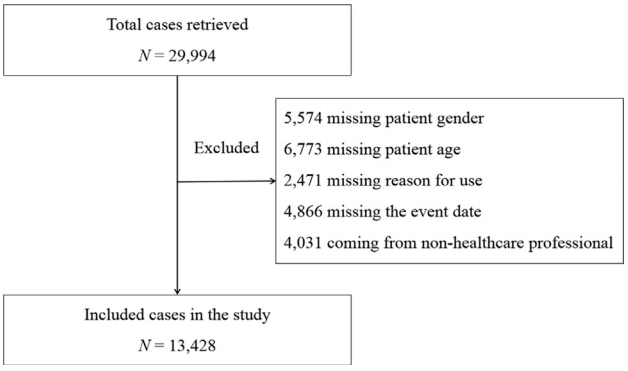

Fig. 1. The exclusion process of included ADRs in this study.

2.3. Time series correlation analysis

We defined X_i, Y_i and Z_i as the time series of total ADRs, fatal ADRs and pharmacogenomic studies, respectively. The cross-correlation coefficients (r) under different time offsets were:

$$r_k(X,Z) = \frac{\sum_{i=1}^{n-k}\left(X_i - \bar{X}_i\right)\left(Z_{i+k} - \bar{Z}_{i+k}\right)}{\sqrt{\sum_{i=1}^{n-k}\left(Xi - \bar{X}i\right)\cdot\sum_{i=1}^{n-k}\left(Z_{i+k} - \bar{Z}_{i+k}\right)}}$$

$$r_k(Y,Z) = \frac{\sum_{i=1}^{n-k}\left(Y_i - \bar{Y}i\right)\left(Z_{i+k} - \bar{Z}_{i+k}\right)}{\sqrt{\sum_{i=1}^{n-k}\left(Yi - \bar{Y}i\right)\cdot\sum_{i=1}^{n-k}\left(Z_{i+k} - \bar{Z}_{i+k}\right)}}$$

Where, $r_k(X,Z)$ and $r_k(Y,Z)$ are the sequence of correlation coefficients between total ADRs, fatal ADRs and pharmacogenomic studies under different time offset k, respectively; n is the sequence length; k is the offset time (0, ± 1, ± 2, …). According to experience, k value is less than or equal to n/4, so the maximum value of k is 7.

3. Result

As shown in Fig. 2, the number of total ADRs gradually increased after irinotecan was approved, and began to decrease after 2018, while the number of fatal ADRs showed a downward trend after 2013. Additionally, the number of pharmacogenomic studies reached the peak in 2017.

When the time offset ranging from 0 to ± 7, Fig. 3 shows that there is a positive correlation between the number of total ADRs and pharmacogenomic studies (0.52–0.78), of which the maximum correlation coefficient was 0.78 (95 % CI: 0.58–0.90), with a lag of 1 year. At the same time, there is also a positive correlation between the number of fatal ADRs and pharmacogenomic studies (0.39–0.87), with the maximum correlation coefficient of 0.87 (95 % CI: 0.73–0.94), with an offset of – 4 years, indicating that

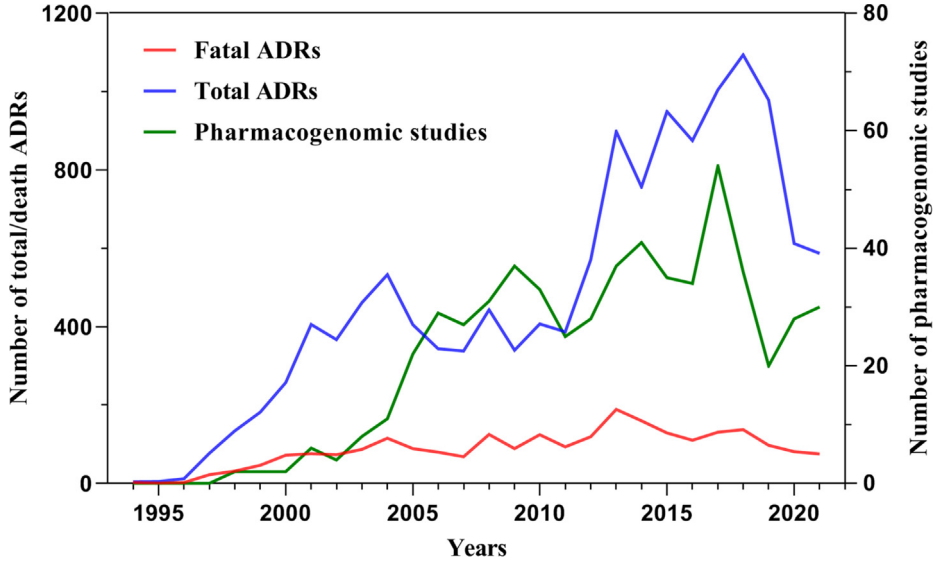

Fig. 2. The annual change trends of total ADRs, fatal ADRs and pharmacogenomic studies.

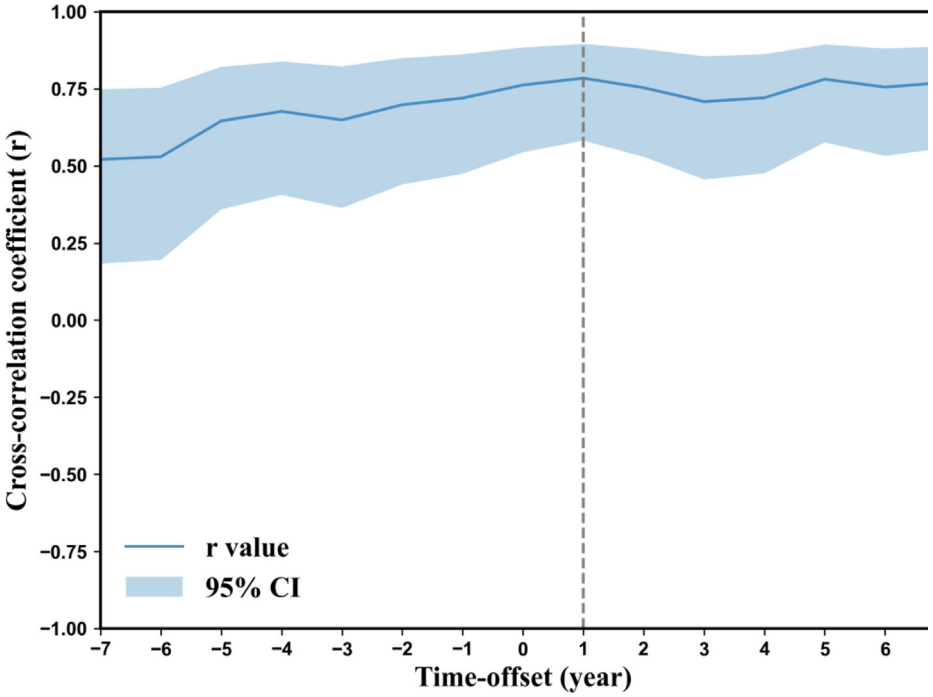

Fig. 3. The time series cross-correlation between the number of total ADRs and pharmacogenomic studies.

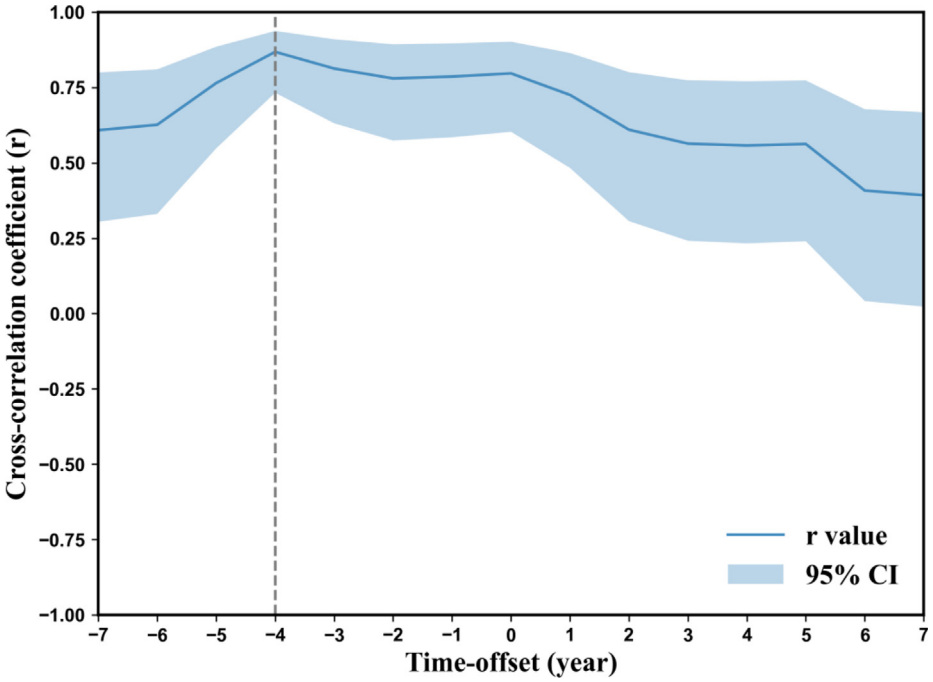

Fig. 4. The time series cross-correlation between the number of fatal ADRs and pharmacogenomic studies.

before the peak of pharmacogenomic studies, the resulting fatal ADRs began to decline 4 years in advance (Fig. 4).

4. Discussion

To our knowledge, this is the first study to investigate the relationship between the ADRs and pharmacogenomic studies using a time-offset cross-correlation method. It was found that both total ADRs and fatal ADRs were significantly positively correlated with trends in the published pharmacogenomic literatures. Interestingly, the time-offset of total ADRs and fatal ADRs were 1 year and − 4 years, respectively, suggesting that pharmacogenomic studies have a faster response time in reducing fatal ADRs during clinical application.

It is undeniable that the number of ADRs is not only affected by the single factor of UGT1A1 gene polymorphism, but also by various factors such as changes in the recommended treatment regimen by the guideline, liposome-encapsulated form and so on (Assiri & Noor 2020, Karas et al 2022, Milano et al 2022). However,

this study provides large-scale real world data support for the important role of UGT1A1 genotype in guiding irinotecan dose in clinical practice, which helps to promote the inclusion of mandatory genetic testing in guideline (Karas & Innocenti 2022), and is worthy of reference for other drugs.

5. Conclusion

Overall, this is the first study to investigate the relationship between the number of ADRs and pharmacogenomic studies using a time-offset cross-correlation method. It was found that the change trend of ADRs was significantly positively correlated with published pharmacogenomic literatures, which confirmed the role of pharmacogenomic research in promoting the safe use of irinotecan in clinical practice.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Ajani, J., D'Amico, T., Bentrem, D., Chao, J., Cooke, D., Corvera, C., Das, P., Enzinger, P., Enzler, T., Fanta, P., Farjah, F., Gerdes, H., Gibson, M., Hochwald, S., Hofstetter, W., Ilson, D., Keswani, R., Kim, S., Kleinberg, L., Klempner, S., Lacy, J., Ly, Q., Matkowskyj, K., McNamara, M., Mulcahy, M., Outlaw, D., Park, H., Perry, K., Pimiento, J., Poultsides, G., Reznik, S., Roses, R., Strong, V., Su, S., Wang, H., Wiesner, G., Willett, C., Yakoub, D., Yoon, H., McMillian, N., Pluchino, L., 2022. Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J. Nat. Compreh. Cancer Network : JNCCN 20, 167–192. https://doi.org/10.6004/jnccn.2022.0008.

Ando, Y., Saka, H., Asai, G., Sugiura, S., Shimokata, K., Kamataki, T., 1998. UGT1A1 genotypes and glucuronidation of SN-38, the active metabolite of irinotecan. Ann. Oncol. 9, 845–847. https://doi.org/10.1023/a:1008438109725.

Argevani, L., Hughes, C., Schuh, M.J., 2020. Dosage adjustment of irinotecan in patients with UGT1A1 polymorphisms: a review of current literature. Innov. Pharm. 11. https://doi.org/10.24926/iip.v11i3.3203.

Assiri, A., Noor, A., 2020. A computational approach to predict multi-pathway drug-drug interactions: a case study of irinotecan, a colon cancer medication. Saudi Pharm. J. 28, 1507–1513. https://doi.org/10.1016/j.jsps.2020.09.017.

Benson, A., Venook, A., Al-Hawary, M., Arain, M., Chen, Y., Ciombor, K., Cohen, S., Cooper, H., Deming, D., Farkas, L., Garrido-Laguna, I., Grem, J., Gunn, A., Hecht, J., Hoffe, S., Hubbard, J., Hunt, S., Johung, K., Kirilcuk, N., Krishnamurthi, S., Messersmith, W., Meyerhardt, J., Miller, E., Mulcahy, M., Nurkin, S., Overman, M., Parikh, A., Patel, H., Pedersen, K., Saltz, L., Schneider, C., Shibata, D., Skibber, J., Sofocleous, C., Stoffel, E., Stotsky-Himelfarb, E., Willett, C., Gregory, K., Gurski, L., 2021. Colon cancer, version 2.2021, NCCN clinical practice guidelines in oncology. J. Nat. Compreh. Cancer Network : JNCCN 19, 329–359. https://doi.org/10.6004/jnccn.2021.0012.

Carrato, A., 2022. Precision medicine: UGT1A1 genotyping to better manage irinotecan-induced toxicity. JCO Oncol. Pract. 18, 278–280. https://doi.org/10.1200/OP.21.00858.

de Man, F., Goey, A., van Schaik, R., Mathijssen, R., Bins, S., 2018. Individualization of irinotecan treatment: a review of pharmacokinetics, pharmacodynamics, and pharmacogenetics. Clin. Pharmacokinet. 57, 1229–1254. https://doi.org/10.1007/s40262-018-0644-7.

Ettinger, D., Wood, D., Aisner, D., Akerley, W., Bauman, J., Bharat, A., Bruno, D., Chang, J., Chirieac, L., D'Amico, T., DeCamp, M., Dilling, T., Dowell, J., Gettinger, S., Grotz, T., Gubens, M., Hegde, A., Lackner, R., Lanuti, M., Lin, J., Loo, B., Lovly, C., Maldonado, F., Massarelli, E., Morgensztern, D., Ng, T., Otterson, G., Pacheco, J., Patel, S., Riely, G., Riess, J., Schild, S., Shapiro, T., Singh, A., Stevenson, J., Tam, A., Tanvetyanon, T., Yanagawa, J., Yang, S., Yau, E., Gregory, K., Hughes, M., 2022. Non-small cell lung cancer, version 3.2022, NCCN clinical practice guidelines in oncology. J. Nat. Compreh. Cancer Network : JNCCN 20, 497–530. https://doi.org/10.6004/jnccn.2022.0025.

Hulshof, E.C., de With, M., de Man, F.M., Creemers, G.J., Deiman, B., Swen, J.J., Houterman, S., Koolen, S.L.W., Bins, S., Thijs, A.M.J., Laven, M.M.J., Hovels, A.M., Luelmo, S.A.C., Houtsma, D., Shulman, K., McLeod, H.L., van Schaik, R.H.N., Guchelaar, H.J., Mathijssen, R.H.J., Gelderblom, H., Deenen, M.J., 2022. UGT1A1 genotype-guided dosing of irinotecan: a prospective safety and cost analysis in poor metaboliser patients. Eur. J. Cancer 162, 148–157. https://doi.org/10.1016/j.ejca.2021.12.009.

Karas, S., Innocenti, F., 2022. All you need to know about UGT1A1 genetic testing for patients treated with irinotecan: a practitioner-friendly guide. JCO Oncol. Pract. 18, 270–327. https://doi.org/10.1200/OP.21.00624.

Karas, S., Mathijssen, R.H.J., van Schaik, R.H.N., Forrest, A., Wiltshire, T., Innocenti, F., Bies, R.R., 2022. Model-based prediction of irinotecan-induced grade 4 neutropenia in advanced cancer patients: influence of demographic and clinical factors. Clin. Pharmacol. Ther. 112 (2), 316–326. https://doi.org/10.1002/cpt.2621.

Kong, L., Rong, L., Wang, M., 2022. Re: UGT1A1 genotype-guided dosing of irinotecan: a prospective safety and cost analysis in poor metaboliser patients: Is it time for everyone treated with irinotecan to be tested for UGT1A1 gene polymorphism? Eur. J. Cancer 170, 194–215. https://doi.org/10.1016/j.ejca.2022.03.044.

Milano, G., Innocenti, F., Minami, H., 2022. Liposomal irinotecan (Onivyde): exemplifying the benefits of nanotherapeutic drugs. Cancer Sci. 113, 2224–2231. https://doi.org/10.1111/cas.15377.

Muthuchellappan R, V J R, Ganne S UR, K T, Jacob A, G S, V B, K M. 2018. Correlation between time lag of arterial-plethysmographic waveforms and systemic vascular resistance: a prospective study. *J Med Eng Technol* 42:18-25. https://doi.org/10.1080/03091902.2017.1409817

Shao, L., Cao, Y., Jones, T., Santosh, M., Silva, L.F.O., Ge, S., da Boit, K., Feng, X., Zhang, M., BéruBé, K., 2022. COVID-19 mortality and exposure to airborne PM2.5: a lag time correlation. Sci. Total Environ. 806, (Pt 3). https://doi.org/10.1016/j.scitotenv 151286.