Development of an AI-based model for predicting chemotherapy adverse events in elderly cancer patients

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Abstract

With the aging of the population in recent years, opportunities to perform chemotherapy for elderly cancer patients have increased. Predicting the risk of adverse events (AEs) of chemotherapy in an elderly patient is very important because the AEs tend to be more severe in this patient group. However, because elderly cancer patients are a heterogeneous population with diverse backgrounds, it is difficult to accurately predict the incidence of AEs. In this study, we investigated the usefulness of artificial intelligence (AI) in predicting chemotherapy AEs in elderly cancer patients. We evaluated the predictive performance of AI regarding the risk of requiring dose modification (dose reduction and/or treatment interruption) due to AEs in elderly cancer patients by training AI about the correlation between clinicopathologic factors and dose modification. Consequently, the area under the curve value of the ROC curve of the AI model was 0.608, indicating that its predictive performance was unsatisfactory. These results may be attributed to the small number of cases, and further studies with a larger number of cases are needed in the future.

1. Aim of Research

As life expectancy increases worldwide, the age of patients with cancer is also expected to increase. Accordingly, the use of chemotherapeutic agents for elderly cancer patients will also increase. Elderly patients are at risk of serious adverse events (AEs) associated with chemotherapy due to the deterioration of organ functions, and therefore, it is important to be careful when administering chemotherapeutic agents to these patients.

Chemotherapy to advanced ovarian cancer has undergone a considerable change with the advent of poly (ADP-ribose) polymerase (PARP) inhibitor therapy. Olaparib, a PARP inhibitor, has proven effective as a maintenance therapy in the initial and recurrent treatment for advanced ovarian cancer and is currently used in clinical practice as the standard care.

Dose modification (dose reduction and/or treatment interruption) of chemotherapeutic agents are performed as appropriate in clinical practice for the purpose of managing AEs. Predicting in advance which patients are at high risk for requiring olaparib dose modification may help clinicians to manage AEs appropriately. Consequently, olaparib could be administered more safely to patients with ovarian cancer. Furthermore, avoiding unnecessary dose modification by predicting the risk of dose modification may lead to preserving the relative dose intensity (RDI) of chemotherapeutic agents and thus maintaining therapeutic efficacy. However, it is difficult to predict which patients will require olaparib dose modification due to AEs.

In recent years, artificial intelligence (AI) has increasingly been used in various fields in medicine. Among the many functions of AI, performing predictive analysis from a large variety of data is the area where AI is particularly adept. Therefore, it is expected that AI could be used to predict chemotherapy AEs in patients with high accuracy based on a large amount of clinical information, but such studies have rarely been conducted to

date.

In this study, we investigated whether AI can predict olaparib dose modification due to AEs in elderly ovarian cancer patients. The development of an AI model that accurately predicts the risk of AEs for elderly cancer patients is expected to enable safe and effective medical care to be provided to elderly cancer patients in the future, and is of great social significance for a better aging society.

2. Method of Research & Progression

2-1 Patients

Patients who were diagnosed histologically with epithelial ovarian cancer (EOC), fallopian tube cancer, or peritoneal cancer, who received maintenance therapy with olaparib from March 2018 to March 2022, were included in this study.

2-2 Treatment and evaluation of adverse events

Olaparib was administered orally each day at a dosage of 600 mg. Olaparib dose modification was implemented according to the discretion of the attending physician to manage AEs, such as grade 3 hematological and non-hematological toxicities. AEs were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

2-3 Statistical analyses

Continuous variables are expressed as the mean ± standard deviation. Patients were categorized according to whether they required dose modification. We compared patients' characteristics and the type and incidence of AEs in each group. We used the chi-square test or Fisher's exact test for the comparisons of categorical variables. We performed a multivariate logistic regression analysis to estimate the odds ratio (OR) with 95% confidence intervals (CIs) for dose modification. We calculated the optimal cutoff values of age for dose modification based on the Youden index from receiver operating characteristic (ROC) curves. Statistical significance was defined as $p < 0.05$. Statistical analysis was performed using JMP Pro 13 software (JMP Pro 13, SAS Institute, Cary, NC, USA).

2-4 AI analyses

AI model are used to predict dose modification in elderly ovarian cancer patients based on various clinicopathologic factors (age, performance status, stage, histologic type, and comorbidities). Prediction models were developed utilizing Prediction One (Sony Network Communications Inc., Tokyo, Japan), which combines neural networks and gradient-boosted decision trees in an ensemble learning approach. Prediction One autonomously fine-tuned and optimized the variables, subsequently generating the optimal prediction model through an artificial neural network that incorporated internal cross-validation. The prediction performance of the AI model is evaluated by the Area Under the Curve (AUC) value of the ROC curve.

3. Results of Research

3-1 Patients' characteristics

From March 2018 to March 2022, olaparib was administered to 60 patients who were diagnosed with EOC. The median follow-up was 20.0 months (interquartile range 14.0–30.0 months). The mean age of the patients was 64.9 ± 11.1 years. The mean weight of the patients was 54.0 ± 10.8 kg. A total of 81.7% of the patients had stage III or IV ovarian cancer. In addition, 20% of the patients received olaparib at the time of initial treatment and 80% at the time of recurrence. A total of 25% of the patients had *BRCA* mutations, and the others had no mutations or unknown.

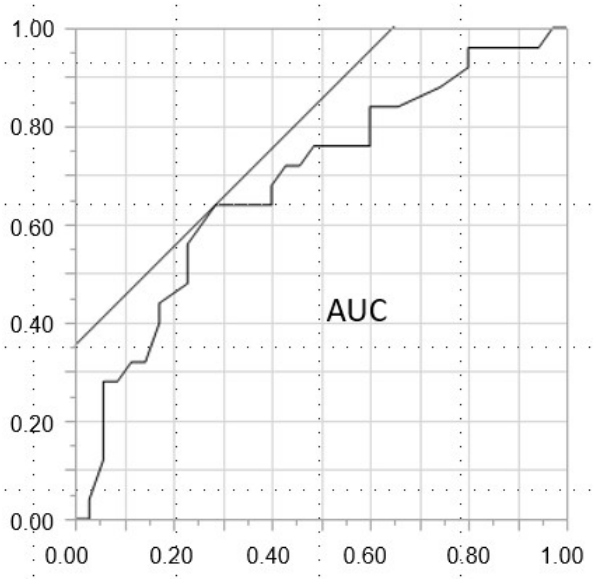
3-2 Dose modification and patients' characteristics

The patients were categorized with or without dose modification. Dose modification was required in 25 of 60 (41.7%) patients. The incidence of grade ≥ 3 anemia and nausea was particularly high in patients who required dose modification compared with those who did not.

We examined whether clinical parameters, such as age, weight, body mass index, treatment status, and comorbidities, were associated with dose modification. Patients who required dose modification

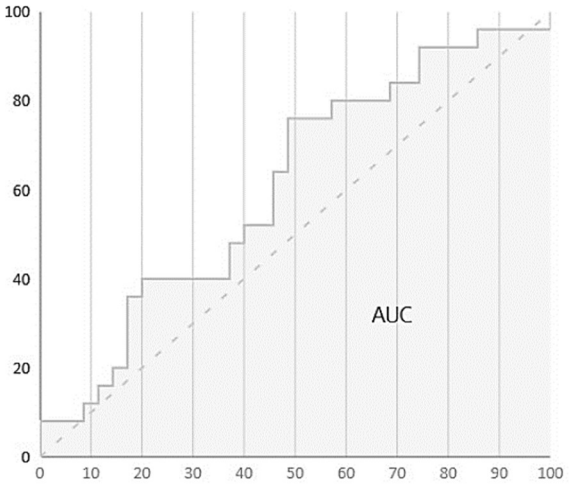
were significantly older compared with those who did not require dose modification (p = 0.018). No other clinical parameters were significantly associated with dose modification. In addition, we examined the association between dose modification and patients' characteristics in the multivariate analysis. Age was significantly associated with dose modification (OR, 1.056; 95% CI, 1.002–1.112; p = 0.034).

We calculated the optimal cutoff values of age for dose modification based on the Youden index from ROC curves. The optimal cutoff value for age was 65.0 years, with a sensitivity of 64.0% and a specificity of 64.6%. The AUC was 0.687 as shown in the following figure.



3-3 AI analysis

The above results indicate that dose modification is often required in the elderly over 65 years of age. AI model predicted dose modification of elderly patients over 65 years old based on various clinicopathologic factors listed above. The AUC was 0.608, as shown in the figure below.



4. Future Area to Take Note of, and Going Forward

This study showed that the risk of requiring olaparib dose modification due to AEs is higher in elderly cancer patients 65 years and older. AI prediction of dose modification in elderly cancer patients did not have sufficient predictive power due to the small number of cases. We plan to increase the number of cases and continue to study the usefulness of AI in predicting chemotherapy AEs in elderly cancer patients.

5. Means of Official Announcement of Research Results

After conducting additional studies as described above, we plan to present the results of this study at a conference and submit them as an article in a medical journal.