MOLECULAR HEALTH
MH GUIDE

Patient case

70-year-old with recurrent ovarian cancer

After several therapies and relapses, a 70-year-old female patient with advanced ovarian cancer experienced renewed progression. The use of Molecular Health Guide (MH Guide) provided the molecular tumor board with comprehensive insights and individual therapeutic recommendations.

Initial diagnosis & therapy: High-grade serous ovarian cancer

In 2012, a 70-year-old female patient was diagnosed with high-grade serous ovarian cancer in stage FIGO IV A. The initial therapy included[1]

- Debulking surgery that led to a complete resection
- Subsequent first-line chemotherapy consisting of six cycles of carboplatin/paclitaxel

Due to familial clusters of malignant tumors, germline BRCA[a] gene testing was performed at the end of 2012, which detected a pathogenic BRCA1 mutation (BRCA1 p.V340fs).[1]

Course of the disease: First recurrence after 4.5 years, followed by others

After 4.5 years of latency, the patient experienced a change in her condition at the end of first-line therapy at the first recurrence of an intra-abdominal tumor. This was followed by:[1]

- Second-line chemotherapy consisting of 6 cycles of carboplatin and pegylated liposomal doxorubicin, which led to complete imaging and serological remission
- Subsequent maintenance therapy with the PARP[b] inhibitor olaparib due to the pathogenic BRCA1 mutation detected in the patient

After a latency of 15 months, there was a second recurrence:[1]

- Third-line chemotherapy consisted of 6 cycles of carboplatin plus gemcitabine, since the VEGF[c] inhibitor bevacizumab had to be avoided due to a newly diagnosed pulmonary artery embolism and the respective approval status.

This therapy led to partial remission and subsequent maintenance therapy with the PARP inhibitor niraparib. The disease progressed again 4 months later.[1]

MH Guide analysis: Three clinically-relevant tumor changes

In June 2019, the patient was approved for tumor genomic panel testing as part of a selective contract between the Techniker Krankenkasse [Technician Health Insurance Fund], Kliniken Essen-Mitte [Essen-Mitte Clinics] and Charité, and a biopsy of the progressed tumor was taken. Using a 613-gene panel (300-fold cover at min. 20% tumor cellularity), NGS data was collected, which was then analyzed with MH Guide in-vitro diagnostic software. Analysis showed 3 clinically-relevant genomic changes:[1]

- Two frameshift mutations in the BRCA1 gene
- One somatic frameshift mutation in the TP53[d] gene
- Tumor mutation burden (TMB) of approximately 27 mutations per megabase (mut/Mb)

Interpretation of gene variants

The MH Guide report made it possible to further differentiate the genomic nature of the tumor. In addition, the MH Guide analysis enabled interpretation of the gene variants:[1]

The two BRCA frameshift mutations may have caused resistance to PARP inhibitors.

The MH Guide analysis confirmed the pathogenic BRCA1 p.V340fs mutation already detected in 2012. The second detected BRCA1 frameshift mutation (p.D330fs) leads to the restoration of the reading frame of the BRCA1 gene, which could partially reactivate the BRCA function.[1,2] This could explain the patient's disease progression under maintenance therapy with niraparib.[1]

The TP53 frameshift mutation is associated with a possible response to bevacizumab.

Pre-clinical evidence is available for the somatic TP53 frame shift mutation as a predictive biomarker for the response to therapy with bevacizumab.[1,3]

The TMB status indicated a possible response to immunotherapy.

The MH Guide analysis classified the determined TMB of 27 mut/Mb as high, since the molecular tumor board had set a limit value of 10 mut/Mb. The user of MH Guide can select a threshold value for TMB depending on the disease in question. Based on scientific knowledge, the MH Guide report showed immunotherapy as a possible treatment option for this patient.[1]

Therapy options for the molecular tumor board

From the identified gene variants, MH Guide derived individual treatment options that were discussed in the molecular tumor board:[1]

- **Mono chemotherapy**, e.g. with paclitaxel **combined with bevacizumab** was now a treatment option, since bevacizumab is approved for ovarian cancer.[4,5] This treatment had to be omitted at an earlier point due to pulmonary embolism.
- As there was no approved immune checkpoint inhibitor therapy for ovarian cancer in Germany, MH Guide suggested **possible recruiting studies** (checkpoint inhibitors, also in combination with chemotherapy and bevacizumab).[6-8]

A reimbursement request was submitted for the patient, since bevacizumab is not approved as fourth-line therapy.[1]

Therapeutic decision of the molecular tumor board

NGS analysis allowed the tumor board to gain a differentiated picture of the genomic changes in the patient's tumor. However, due to co-morbidities and the patient's significantly reduced general condition, the therapeutic option identified could no longer be used.[1]

Conclusions from the patient case[1]

- MH Guide enables the creation of a molecular pathological tumor profile and the identification of clinically-relevant biomarkers.
- From this, therapeutic recommendations are derived which support treating physicians in their evidence-based decision-making.
- Patients can especially benefit if the NGS analysis and the MH Guide assessment are used early on, thus allowing the potential of precision medicine in oncology to be deployed in the best possible way.

Abbreviations

a Breast cancer gene

B Poly (ADP-ribose) polymerase

c Vascular endothelial growth factor

d T umor protein p53

Sources

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