GU Highlights - Setting a new standard in urothelial cancer

The data presented will undoubtedly change the first-line treatment of advanced urothelial carcinoma. In addition, interesting data were shown for radioligand 177Lutetium therapy in chemonaive metastatic castration-resistant prostate cancer.

EV302 - Enfortumab vedotin + Pembrolizumab as First Line Therapy in Urothelial cancer

This practice changing trial presented by Thomas Powles tested the antibody-drug conjugate (ADC) enfortumab vedotin (EV; any number of times until progression) in combination with pembrolizumab (maximum of 35 cycles) against platinum-based chemotherapy with gemcitabine (up to 6 cycles) in first-line advanced unresectable or metastatic urothelial carcinoma (1). In the control arm, both cisplatin and carboplatin were permitted and one third of the patients received switch maintenance immunotherapy. With a median progression-free survival of 12.5 over 6.3 months the median overall survival (OS) was almost doubled in the EV + pembrolizumab arm (31.5 vs. 16.1 months, HR 0.47). The overall response rate (ORR) was 67.7 % including 29.1 % complete remissions. Basically, each prespecified subgroup benefited equally from EV + pembrolizumab regardless of cisplatin eligibility, PDL1 expression and presence of liver metastases. These results thus eclipsed the also positive phase 3 study Checkmate 901, which tested the addition of nivolumab simultaneously to cisplatin/gemcitabine and also showed a survival advantage (median OS 21.7 vs. 18.9 months, HR 0.78) and thus - after several other phase 3 studies remained negative overall - the advantage of concurrent immunotherapy for the first time (2). This means that EV + pembrolizumab will become the new standard for advanced urothelial carcinoma and the further treatment sequence will have to be redefined accordingly. In everyday clinical practice, we will have to learn to deal with the typical side effects of EV - in particular skin toxicity, peripheral neuropathy and hyperglycemia. Treatment-related grade 3 and above toxicity was reported at 55 versus 70 % in the chemotherapy arm. In addition, the challenging question arises as to how long enfortumab vedotin should actually be administered in view of the high complete remission rates, the toxicity profile and, last but not least, the substantial costs.

PSMAfore - 177Lutetium radioligand therapy in metastatic castration-resistant prostate cancer

Radioligand therapy with 177Lutetium PSMA617 has been approved in Switzerland in the third line of therapy for patients with metastatic castration-resistant prostate cancer who have already received chemotherapy with docetaxel and an androgen receptor pathway inhibitor (APRI). The approval is based on phase 3 data from the VISION Trial, which showed a significant advantage for the beta emitter 177Lutetium over standard of care (SOC) (ARPI, steroids, or radiotherapy) in various endpoints, including overall survival (3). On the other hand, not every patient qualifies for or refuses chemotherapy with docetaxel. Oliver Sartor presented phase 3 data on patients who had been pretreated with an ARPI - either in the hormone-sensitive or castration-resistant setting - and were now randomized to 6 cycles of 177Lutetium or another ARPI (abiraterone or enzalutamide) (4). The data shown is based on the second interim analysis. The primary endpoint radiographic progression-free survival (rPFS) was significantly prolonged in the experimental arm (median rPFS 12 vs. 5.5 months, HR 0.43) along with various other endpoints (PSA response, time to pain progression, time to first symptomatic skeletal event). However, the preliminary data on overall survival show no difference between the groups (median OS 19.2 and 19.7 months respectively). Treatment- related adverse events grade 3 and above were reported at 33 % (including anemia, dry mouth) and 43 % in the change of ARPI arm respectively. Undoubtedly the primary endpoint was met, although rPFS is only a modest endpoint in a rather early disease situation. It can be assumed that the mere fact of being able to (temporarily) avoid chemotherapy will lead to the use of 177Lutetium PSMA617 in this disease setting. Nevertheless, the study has weaknesses and raises questions. In particular, the control arm is weakly chosen, as it is known that two ARPI sequentially do not result in a high response probability due to cross resistance. Since almost no patients with liver metastases were included, no statement can be made here about these or about patients with dynamic symptomatic disease. In addition, the number of 177Lutetium cycles actually required remains unanswered.

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Referenzen:

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