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Cytoreductive Nephrectomy Would Not Be Required In Intermediate and Poor Risk Patients with Metastatic Renal Cell Carcinoma Cancer

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Short Communication

To date, cytoreductive nephrectomy before systemic therapy is generally recommended in patients with a potentially surgically resectable primary Renal Cell Carcinoma (RCC) and multiple metastases. Targeted therapy with tyrosine kinase inhibitors is widely used in the first-line treatment of metastatic renal cell carcinoma. The objective of CARMENA study was to determine whether cytoreductive surgery before the initiation of the targeted therapy in patients with metastatic Renal Cell Carcinoma (mRCC) is required.

20-Year-Old Standard

During the past 20 years it was believed that primary tumor resection in patients without a history of nephrectomy significantly improves the results of subsequent systemic therapy. This mainstay of therapy was adopted in the cytokine's era after the publication of the results of two studies that confirmed the need of cytoreductive nephrectomy before interferon treatment [1,2]. Therefore, inclusion criteria of the most studies of targeted agents traditionally contained cytoreductive nephrectomy or history of nephrectomy. Large meta-analyses and retrospective studies that included thousands of patients have unanimously found that primary tumor resection before targeted treatment is essential. Doubts expressed by certain groups and in a few studies [3-5], in particular those concerning the inexpediency of nephrectomy in poor risk patients, were ignored, and the recommendations, such as those by NCCN [6], remained unchanged. And now the CARMENA study is performed [7] that have set the things straight.

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The CARMENA Study

The intermediate and poor risk patients, according to the MSKCC criteria, were randomized into a cytoreductive nephrectomy group with further sunitinib treatment (N=226) or a sunitinib alone group without a primary tumor resection. The study had a noninferiority design, thus its objective was to prove a similar efficacy of both approaches. The hazard ratio of the risk of death in the groups was not to exceed 1.2, and the conclusion of similar efficacy could be made only in this case.

The median values for primary tumor size and total tumor mass, including metastases, were 8.8/8.6 cm and 14/14.4 cm in nephrectomy+sunitinib / sunitinib alone groups, respectively. The most common sites of metastases were lungs (>70%), lymph nodes (35-39%), and bones (36-37%). In 6.7% of the patients randomized in the combined treatment group, cytoreductive treatment could not be performed; 17.7% of the patients could not receive sunitinib. In the second group, 4.9% of the patients did not receive sunitinib and nephrectomy was performed in 17%. In case of disease progression in both groups, the further treatment was performed in half of the patients and it was similar (everolimus or axitinib).

With a median follow-up time of 50.9 months, the hazard ratio of the risks of death in the groups was 0.89, thus the HR did not exceed the predetermined value of 1.2, signifying the equal life span of patients with or without cytoreductive nephrectomy. The median overall survival was even better in patients receiving sunitinib alone, 18.4 month versus 13.9 months in nephrectomy with further sunitinib treatment group. The trend was observed in both the intermediate risk group (23.4 months versus 19 months, HR = 0.92) and the poor risk group (13.3 months versus 10.2 months, HR = 0.86).

The median progression-free survival was 8.3 months in the sunitinib alone group and 7.2

months in the nephrectomy group (HR = 0.82). Objective response rate was nearly similar - 29.1% and 27.4%, respectively. Disease control (the sum of complete responses, partial responses and stable disease) for 12 weeks and longer was significantly better in the group without surgical treatment - 47.9% versus 36.6% (P = 0.02). Moreover, the patients, in whom the primary tumor was not resected, have received sunitinib for a longer period (8.5 months) as compared to post-nephrectomy patients (6.7 months, P = 0.04). The incidence of grade 3-4 adverse events was higher in the sunitinib alone group, in which it was 42.7%; 32.8% of patients had grade 3-4 toxicity in nephrectomy plus sunitinib group (P = 0.04).

How would the Study Results Influence the Routine Practice?

Of course, the results of the CARMENA study may be considered positive: the primary endpoint of no differences in survival was achieved. Thus, cytoreductive nephrectomy before sunitinib initiation would not necessarily be beneficial in intermediate or poor risk mRCC patients. The study shows that therapy with sunitinib in mRCC patients should be started as early as possible, as a delay may lead to a lower disease control and make the duration of sunitinib treatment shorter. In the nearest future we may expect changes in the practical guidelines. Intensive discussion of the study behind the scenes showed that some urological oncologists would not be ready to immediately abandon the tactics accepted earlier and would continue to perform nephrectomy before systemic treatment. They could be right in some circumstances. For example, in patients with macrohematuria, pain, uncontrolled hypertension and paraneoplastic syndrome nephrectomy will remain meaningful. Nephrectomy would be palliative in these cases. It is unclear whether in favorable risk patient's surgical treatment is required. Dr. Daniel George of Duke University, who commented on the study at 2018 ASCO Annual Meeting [8], has proposed that CARMENA results may be extrapolated at the total patient population. However, if evidence-based medicine principles are to be followed strictly, the effect of not performing cytoreduction in the favorable risk group was not proved. What is to be done with patients with non-clear cell carcinoma in whom first-line sunitinib is also the drug of choice for intermediate risk? Several month ago the results of another large retrospective IMDC analysis were presented at GU ASCO Meeting [9], which showed that cytoreductive nephrectomy in metastatic papillary renal cancer increases overall survival by a factor of 2 from 8.6 to 16.3 months (HR=0.62, P<0.0001) with a restriction of worse results in the poor risk group.

Of interest is the question of whether nephrectomy is needed before treatment with other agents: temsirolimus (first-line treatment standard in poor risk group with clear-cell and non-clear-cell mRCC [10]), combination of nivolumab and ipilimumab (recently approved in the US as a first-line treatment in intermediate and poor risk patients [11]), cabozantinib (first-line treatment option in intermediate and poor risk patients based on the results of CABOSUN study [12]). In general, how would the study results influence the choice of the first-line treatment? Would sunitinib, which demonstrated better results in poor risk patients, be prescribed more frequently than temsirolimus [13]? If the patient presents with a non-resected primary tumor and intermediate/poor risk, what will the physician choose: immediate sunitinib treatment or one-month interval for the patient to perform a cytoreductive surgery and checkpoint inhibitors treatment after one month? Should a different approach be considered when the primary tumor in patient remains after the first-line sunitinib treatment: should one consider cytoreductive nephrectomy before the second-line treatment with nivolumab, axinitinib or lenvatinib combined with everolimus? All these medications were studied mainly in patients after a nephrectomy [14-16].

We have suddenly encountered a change of the treatment standard of mRCC and many questions have arisen. However, after the CARMENA study results were presented, there is no doubt that cytoreductive nephrectomy is not required in intermediate/poor risk patients mRCC. Cytoreductive nephrecromy does not increase the overall survival or progression-free survival or response to further targeted therapy and, moreover, is associated with possible surgical complications and additional costs. Nevertheless, trial results are not relevant to the patients with a poor performance status, lung metastasis only, and minimal volumes of metastatic disease, because population of these patients was not representative in CARMENA study.

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