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Revolutions in cancer treatment:
how can they be integrated?

Gastrointestinal cancers

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Abstract

Although immunotherapy has led to major advances in the treatment of melanoma and lung cancer, the same is not true for gastrointestinal cancers, which account for 25% of solid tumours and represent a very heterogeneous group of cancers. The major breakthrough facilitated by immunotherapy is mainly in subgroups of gastrointestinal tumours that have a phenotype of microsatellite instability (MSI). The use of immune checkpoint inhibitors (ICIs) in patients with the MSI phenotype seems to hold promise irrespective of the type of gastrointestinal tumour. For gastrointestinal cancers with a microsatellite stable (MSS) phenotype, the main advances have been reported in gastric cancers and hepatocellular carcinoma. For immunotherapy to be effective in other gastrointestinal cancers, a combined approach may be required, first using drugs other than ICIs to restore a local immune reaction and then to use ICIs against the immunoresponsive tumour. A number of trials are underway using this type of strategy (ICIs combined with growth factors, anti-tumour vaccines etc.).

COLORECTAL CANCER

Gastrointestinal tumours account for about 25% of all solid tumours. The most common gastrointestinal cancer is colorectal cancer, with about 40,000 cases a year in France. Among colorectal cancers, microsatellite instability (MSI) is present in 5% of stage 4 (metastatic) tumours, 10% of stage 3, and 20% of stage 1 and 2 tumours. These MSI tumours occur either in the context of Lynch syndrome or sporadically. MSI tumours are characterised by a large number of mutations within the tumour and a high mutation load, which leads to the creation of numerous neoantigens. Such tumours are characteristically infiltrated by lymphocytes, but the immune infiltration is not sufficient to control tumour progression.

A notable study was carried out in 41 patients with i) colon cancer with MSI or ii) colon cancer without microsatellite instability (MSS), or iii) MSI tumours that were not colorectal. This study provided extremely strong proof of concept that MSI tumours, whether they are colorectal or not, respond better to pembrolizumab than MSS tumours do.[1] The authors then evaluated the efficacy of PD-1 blockade for 12 different types of MSI tumours and confirmed that patients with an MSI phenotype had a strong response rate to immunotherapy.[2] The phase 3 Keynote-177 (NCT02563002) study is evaluating progression-free survival in 270 patients with metastatic MSI colorectal tumours treated either with pembrolizumab or with reference first-line chemotherapies (mFOLFOX6, FOLFIRI), and results will probably be reported in 2020.

Combinations of immunotherapies have also been investigated, for example in the multi-cohort phase 2 CheckMate-142 studies, which evaluated the efficacy and safety of treatments based on nivolumab in patients with metastatic colorectal tumours. In these studies, patients received nivolumab 3 mg/kg, either as monotherapy or combined with ipilimumab (1 mg/kg) every 3 weeks, or a combination of nivolumab plus ipilimumab every 6 weeks (as first-line treatment). The response rate among the 74 patients treated with monotherapy was 31% (69% of the patients showed tumour control); the response rate was 51% in patients on dual therapy not used as the first line of treatment (80% of the 84 patients had tumour control). The response rate among the 44 patients receiving first-line dual therapy with the adapted dose was 60%, with a disease control rate of 85%.[3, 4] These immunotherapy results are interesting, but similar response and tumour control benefits have been obtained with chemotherapy (FOLFIRINOX).[5] On the other hand, the survival curves for dual therapies seem to show a plateau effect, indicating long-term control or even remission in a number of patients. These are exceptional results for this type of cancer, for which the only curative options once it is metastatic are surgery or stereotactic radiotherapy, but not chemotherapy. Confirmatory trials in a larger number of patients are required. This study also showed that dual therapy was well tolerated when ipilimumab was taken every 6 weeks; the profile of grade 3-4 events was similar or even lower than in the group receiving nivolumab monotherapy.[3, 4]

A number of questions still remain unanswered for patients with MSI colorectal cancers, 16% of whom are immediately refractory to ICI and show progression at the first evaluation, and 25% of whom progress within the first year. Is it necessary to use immunotherapy as the first line of treatment, since chemotherapies usually control the disease well for the first year? Should a combination be used first-line or only after the patient has developed resistance to monotherapy with an agent targeting programmed death ligand-1 (PD-L1)? What is the right treatment regimen and what is the optimal duration of treatment? Clinical trial data are limited, so should we be offering these combinations now, without a randomised study? Finally, how can primary and secondary resistance to immunotherapy be overcome?

Patients with MSS colorectal cancers account for 95% of metastatic colorectal cancers. One study has shown a positive efficacy trend using the combination of an agent targeting cytotoxic T-lymphocyte antigen 4 (CTLA4; in this case tremelimumab) and an anti-PD-L1 (durvalumab) compared with best palliative care in 180 patients with colorectal cancer who had been extensively pretreated and were refractory.[6] Analysis of subgroups in this study showed better overall survival among the patients whose tumours had a high mutation load compared with patients with a low mutation burden. This result, from a small study with a limited number of patients, suggests that a large mutation load could be a predictive marker of the efficacy of immunotherapy, making it possible to select MSS patients who may benefit from this treatment in the future.

What is the best way to select patients with MSS colorectal cancer? A small number of "hypermutated" patients present with polymerase E and D deficiencies, and preliminary data indicate that these patients seem to respond well to immunotherapy. However, more data in larger patient groups are needed and it will probably be necessary to include this MSS sub-population within the group of MSI patients. The Immunoscore® test identifies patients who have lymphocytes within the tumour and trials are being carried out to evaluate the relevance of this. Trials are being conducted on using genomic classification of Consensus Molecular Subgroups (CMS) to identify patients with different prognoses with different prognoses, such as the CMS4 subgroup. Unfortunately, selecting patients by genomic analysis is currently not yet part of our routine practice in colorectal cancer.

How can a colorectal tumour be made immunosensitive? A small study has shown that treatment with MEK inhibitors stimulated lymphocyte infiltration of cancer cells but a phase 3 study combining immunotherapy with MEK inhibitors had negative results.[7] Similarly, combining ICIs with anti-angiogenic immunomodulators or chemotherapy that induces the death of immunogenic cells has proven to be ineffective. The combination of ICIs with radiotherapy to induce an abscopal effect is also being evaluated.

GASTRIC CANCERS

An initial positive phase 3 trial showed the efficacy of nivolumab for patients with chemoresistant gastric cancers.[8] However, this study was conducted in Asian patients, whose gastric cancer differ from those in Western countries, if only in terms of survival (the survival curves go from 60% to 75% with adjuvant treatments for gastric cancer in Japan, compared with 20% to 30% in Europe). One phase 2 study showed that pembrolizumab monotherapy had promising efficacy in patients with advanced stomach or gastro-oesophageal junction cancer who had previously received at least two lines of treatment,[9] but all the phase 3 studies with follow-up were negative.[10-12] Therefore, the data to date indicate that immunotherapy does not have a very clear effect in non-Asian, non-selected patient populations.

How can patients be better selected? More patients with gastric cancers than colorectal cancer have an MSI phenotype, and it is possible that immunotherapy may be more effective in this MSI population. Similarly, it seems that patients with a rather uncommon histological tumour type, induced by the Epstein-Barr virus, show a positive and lasting response to immunotherapy.[13] Finally, a phase 2 study had very promising results in 37 patients presenting with human epidermal growth factor receptor 2 (HER2)-positive gastric tumours; 100% of patients had tumour control or regression after treatment with a combination of pembrolizumab plus trastuzumab.[14] A phase 3 study with this combination is currently underway.[15]

CANCERS OF THE OESOPHAGUS

An Asian study (Attraction-3) has shown that nivolumab was associated with a significant improvement in overall survival and a favourable safety profile compared with chemotherapy in patients previously treated for advanced epidermoid carcinoma of the oesophagus,[16] so nivolumab could represent a second-line treatment option for these patients. In the KEYNOTE-181 phase 3 study, second-line treatment with pembrolizumab for advanced oesophageal cancer did not improve overall survival in the population as a whole compared with chemotherapy, but it improved survival in the 35% of patients in the study who had a combined positive score (CPS) for PD-L1 expression ≥10.[17] However, the CPS is calculated as the total number of PD-L1-positive cells (tumour cells, lymphocytes, and macrophages), divided by the number of viable tumour cells, and multiplied by 100, and is difficult to reproduce. A large number of immunotherapy studies involving anti-CTLA4 (ipilimumab), anti-PD-1 (nivolumab, pembrolizumab) and anti-PD-L1 (durvalumab, atezolizumab, avelumab) agents are currently in progress.

HEPATOCELLULAR CARCINOMA

A randomised phase 3 trial (CheckMate 459, NCT02576509) evaluated nivolumab versus sorafenib as first-line treatment in 742 patients with non-resectable hepatocellular carcinoma. This study did not reach statistical significance for its primary endpoint of overall survival. Pembrolizumab was also compared with placebo, as a second-line treatment after the failure of sorafenib in 413 patients with hepatocellular carcinoma. Once again, the study was negative for the main efficacy endpoints of overall survival and progression-free survival.[18]

On the other hand, a phase Ib study showed that, compared with atezolizumab monotherapy, the combination of atezolizumab plus the anti-angiogenic drug bevacizumab is more effective in terms of progression-free survival.[19] A phase 3 study therefore compared dual therapy using atezolizumab plus bevacizumab with sorafenib monotherapy as first-line treatment.[20] The median overall survival has not yet been reached for the dual therapy arm, but was 13.2 months for the patients randomised to sorafenib. The overall response rate was 27% with dual therapy compared with 12% with sorafenib. These results will probably lead to approval for a new first-line treatment option for hepatocellular carcinoma: the combination of immunotherapy + an anti-angiogenic agent.

CONCLUSION

Immunotherapy has proven to be a major advance in oncology, but the results achieved in patients with gastrointestinal cancers are less marked. For colorectal cancers, immunotherapy seems to be an attractive option for patients with the MSI phenotype. For patients without an MSI phenotype, some interesting data have been reported in gastric cancers, but without a very clear effect in non-selected, non-Asian populations. Meanwhile, for patients with hepatocellular carcinoma, the option of immunotherapy combined with an anti-angiogenic will likely soon be authorised as a first-line treatment.

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