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NOVELTIES IN IMMUNOTHERAPY OF ESOPHAGEAL AND STOMACH CANCER

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Summary

A high frequency of somatic mutations has been detected in stomach and esophageal cancers which makes them a possible suitable target for the application of immunotherapy. Contemporary immunotherapeutic approaches rely on monoclonal antibodies that inhibit immune checkpoints. The results of early clinical studies are promising, while only a few phase III studies have published their results so far. A particulary promising treatment strategy is the combination of checkpoint inhibitors with other treatment modalities, such as chemotherapy, targeted therapy, radiotherapy or T cells agonists.

KEY WORDS: *Esophageal cancer, gastric cancer, checkpoint inhibitors, immunotherapy*

NOVOSTI U IMUNOTERAPIJI TUMORA JEDNJAKA I ŽELUCA

Sažetak

U karcinoma jednjaka i želuca je nađena visoka učestalost somatskih mutacija što ih čini pogodnom metom za primjenu imunoterapije. Suvremeni pristupi u liječenju imunoterapijom temelje se na inhibiciji imunoloških kontrolnih točaka monoklonskim protutijelima. Rezultati kliničkih studija ranih faza su obećavajući dok je svega nekoliko studija faze III do sada objavilo svoje rezultate. Osobito je obećavajuća strategija liječenja kombinacijom inhibitora kontrolnih točaka s drugim modalitetima liječanja poput kemoterapije, ciljane terapije, radioterapije ili terapije agonistima T stanica.

KLJUČNE RIJEČI: *Karcinom jednjaka, karcinom želuca, inhibitori kontrolnih točaka, imunoterapija*

Introduction

Gastric cancer is the third leading cause of cancer-related death in the world with five year survival rate of 29%, while esophageal cancer is the sixth leading cause of cancer-related death in the world with five year survival rate of 18% (1,2). Such low and unsatisfactory survival rates are a consequence of a late diagnosis as well as low number of available efficient therapies for treatment of these diseases. The results of gene analysis of these tumors gave the additional stimulus to explore new therapeutic potentials when four different subtypes of stomach adenocarcinoma as well as three subtypes of squamous cell esophageal carcinoma have been recognized. (3,4). Esophageal adenocarcinoma and subtype of gastric cancer characterized by chromosomal instability seem to be the same disease at the molecular level (5). Despite these differences, stomach and esophageal cancers share common feature which is a high prevalence of somatic mutations that makes them a suitable target for the application of immunotherapy (6). The use of immunotherapy in other tumors with high prevalence of mutations, such as melanoma and lung cancer, has

shown good efficacy with a much longer response to treatment than the use of a standard chemotherapy.

Malignant tumors escape the host immune system by numerous mechanisms, including increasing number of immunosuppressive cells in the tumor environment [regulatory T lymphocytes (Treg), myelod-derived suppressor cells (MDS)], cytokine levels [transforming growth factor β (TGF-β), interleukin 10 (IL-10), indoleamine 2,3-deoxygenase (IDO)] and inhibitory signal pathways of immune checkpoints [cytotoxic T-lymphocyte associated protein-4 (CTLA-4), programmed cell death protein-1 (PD-1), lymphocyte activation gene 3 (LAG3), T cell immunoglobulin and mucin domain-containing molecule-3 (TIM-3)] (7). PD-1 inhibits T cells function by binding to its ligands PD-L1 and PD-L2 while CTLA-4 inhibits T cells by binding to CD80 and CD86. CTLA-4 is important in early, and PD-1 and PD-L1 in late immune response. Current immunotherapeutic approaches rely on monoclonal antibodies that inhibit immune checkpoints. Numerous studies with immune checkpoint inhibitors are in progress (8). Gastric cancer associated with Epstein-Barr virus (EBV) and gastric cancer subtype characterized by microsatellite instability (MSI) are particularly suitable for the treatment with checkpoint inhibitors due to increased expression of PD-L1 and PD-L2 (8).

Immunotherapy of esophageal and stomach cancer

After failure of standard therapy in patients with advanced or metastatic esophageal cancer, independent of the histological subtype, pembrolizumab (anti-PD-1) showed an objective response in 30.4% of patients and stabilization of the disease in additional 13% of patients (KEYNOTE-028, phase Ib) (9). The response was higher in adenocarcinoma (40%) than in squamous cell carcinoma (29.4%). Median duration of response was 40 weeks, and one year progression free survival (PFS) was 21.7%.

Nivolumab (anti-PD-1) was tested (ONO-4538/BMS-936558) in patients with advanced esophageal squamous cell carcinoma who failed standard treatments (10). In that phase II study nivolumab showed an objective response of 17.2% with median survival rate of 10.8 months. Additionally, 25% of patients had stable disease by independent review and 31.3% by investigator assessment. The clinical benefits rates were 42% and 53% respectively.

Based on promising results of phase II trials, two phase III trials of PD-1 blockade in esophageal cancer are ongoing (8). KEYNOTE-181 examines pembrolizumab versus standard second line therapy (taxane or irinotecan) for advanced esophageal and gastroesophageal junction (GEJ) cancers while the other (NCT02569242) compares nivolumab with taxane based second line chemotherapy for unresectable advanced and recurrent esophageal cancer. In addition, currently ongoing CheckMate-577 phase III study examines the adjuvant application of nivolumab versus placebo in operated patients with esophageal cancer and GEJ cancer. Primary aims of the study are disease free survival (DFS) and overall survival (OS). In phase II study (NCT02520453) durvalumab, an anti-PD-L1, has been compared with placebo in operated squamous cell carcinomas (8).

Pembrolizumab, nivolumab, avelumab and durvalumab demonstrated their efficacy in the treatment of stomach and GEJ cancers in phase I and II clinical trials (11-14). The use of pembrolizumab in patients with PD-L1 positive gastric cancer (KEYNOTE 012 trial) showed an objective response in 22% of patients by central assessment with a median duration of response of 40 weeks (15). Median survival rate was 11.4 months. The phase I/II CheckMate-032 trial demonstrated efficacy of nivolumab in the treatment of advanced and metastatic gastric cancer (16). The objective response rate was 14%, irrespective of PD-L1 status. The one-year survival rate was 36%. This trial also assessed the combination of nivolumab and ipilimumab (17). The best clinical activity and median OS were detected in the group treated with nivolumab 1 mg/kg and ipilimumab 3 mg/kg.

Results of the ONO-4538-12 (phase III) trial demonstrated that nivolumab significantly reduced the risk of death by 37% [hazard ratio (HR) = 0.63; $p < 0.0001$] in patients with previously treated advanced gastric cancer refractory to standard therapy (18). The 12-month OS in the nivolumab group was 26.6% versus 10.9% in the placebo group. An objective response rate was 11.2% in patients treated with nivolumab compared to 0.0 % in patients treated with placebo. A median duration of response was 9.53 months.

It should be emphasized that the most of phase III studies are still ongoing and their results are expected (8,11,14). These studies include KEYNOTE-061 trial of pembrolizumab versus paclitaxel after progression to platinum and fluoropyrimidine based chemotherapy; KEYNOTE-062 trial of pembrolizumab monotherapy versus combination of pembrolizumab with cisplatin and 5-fluorouracil (5-FU) or cisplatin and 5-FU alone for the treatment-naïve disease; CheckMate-649 trial of nivolumab plus ipilimumab verus oxalipatin plus fluoropyrimidine in patients with previously untreated advanced or metastatic gastric or GEJ cancers (19); JAVELIN Gastric 100 of avelumab versus oxaliplatin-fluropyrimidine doublet in the first-line setting; and JAVELIN Gastric 300 of avelumab versus physician's choice (irinotecan, paclitaxel or best supportive care) in the third-line setting.

Not only combinations of different checkpoint inhibitors but also combinations of checkpoint inhibitors with T cell agonists, chemotherapy, radiotherapy or targeted therapy have been studied in esophageal and stomach cancers with the intention of achieving a better response (8). Radiotherapy not only has a profound effect on the tumor immune microenvironment in the irradiated region, but can also induce anti-tumor immune responses at distant sites (abscopal effect) (20,21).

In addition, the application of immunotherapy directed against tumor-related antigens such as melanoma 3 (MAGE-A3) and NY-ESO-1 antigen has been investigated, as MAGE-A3 is found in 90% and NY-ESO-1 in 40-90% of esophageal cancers. Clinical studies with vaccines and adoptive cellular immunity are also ongoing (22).

IMAB362 is a chimeric monoclonal antibody against claudin 18.2, a tight junction protein that is expressed in about 70-80% of gastric cancers and also in some other tumors like bile duct and pancreatic cancers. IMAB362 mediates cell killing by antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) (23). In FAST phase II trial combination of IMAB362 and standard chemotherapy (epirubicin, oxaliplatin, capecitabine; EOX) showed better median PFS (7.9 versus 4.8 months, HR = 0.47, $p < 0.0001$), median OS (13.2 versus 8.4 months, HR = 0.51; $p = 0.0001$) and higher objective response rate (39% versus 25%) than chemotherapy alone (24). To be eligible for the study at least 40% of patients' tumors cells had to show an immunohistochemical expression of claudin 18.2 of at least 2+.

CONCLUSION

Intensive research and implementation of immunotherapy in recent years has led to new insights and at the same time has opened up many issues. New immune-related response criteria (irRCs) has been developed to comprehensively capture all response patterns (25). A need for identification of reliable predictive biomarkers has been recognized in order to reduce unnecessary exposure to the side effects in patients who would not respond to treatment as well as unnecessary costs (26). Data concerning PD-L1 expression as a potential biomarker for therapy with checkpoint inhibitors in esophageal and gastric cancer are contradictory and differ from study to study. This is due to the application of different antibodies and various criteria for evaluating expression results, applying fresh or archive tissue samples, determining expression either on tumor cells, or/and on tumor-infiltrating immune cells. In addition to the need for standardization of these tests, it is also necessary to explore and understand the mechanism of the resistance to immunotherapy.

REFERENCES

1. Globocan.iarc.fr. Accessed on 4th February, 2017.
2. www.cancer.net. Accessed on 2th February, 2017.
3. Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. Nature. 2017;541(7636):169-75.
4. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513(7517):202-9.
5. Romero D. Genetics: Oesophageal cancer - not all alike. Nat Rev Clin Oncol. 2017;14(3):138.
6. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science. 2015;348(6230):69-74.
7. Sun W, Yan L. Gastric cancer: current and evolving treatment landscape. Chin J Cancer. 2016;35(1):83.
8. Pectasides E, McDermott D. PD1 and PD-L1 immune checkpoint inhibitors in gastrointestinal cancer. In: Kerr D, Johnson R, editors. Immunotherapy for gastrointestinal cancer. Switzerland: Springer; 2017. p. 115-125.
9. Doi T, Piha-Paul SA, Jalal SI, Mai-Dang H, Yuan S, Koshiji M, Csiki I, Bennouna J. Pembrolizumab (MK-

3475) for patients (pts) with advanced esophageal carcinoma: Preliminary results from KEYNOTE-028. J Clin Oncol. 2015;13:(suppl; abstr 4010).
10. Kojima T, Hara H, Yamaguchi K, Hironaka S, Iwasa S, Kato K, Tsushima T, Yasui H, Ura T, Muro K, Satoh T, Doki Y, Ohtsu A, Hamamoto Y, Kitagawa Y. Phase II study of nivolumab (ONO-4538/BMS-936558) in patients with esophageal cancer: Preliminary report of overall survival. J Clin Oncol. 2016;13: (suppl 4S; abstr TPS175).
11. Bilgin B, Sendur MA, Bülent Akıncı M, Şener Dede D, Yalçın B. Targeting the PD-1 pathway: a new hope for gastrointestinal cancers. Curr Med Res Opin. 2017: 1-11.
12. Raufi AG, Klempner SJ. Immunotherapy for advanced gastric and esophageal cancer: preclinical rationale and ongoing clinical investigations. J Gastrointest Oncol. 2015;6(5):561-9.
13. Jackie Oh S, Han S, Lee W, Lockhart AC. Emerging immunotherapy for the treatment of esophageal cancer. Expert Opin Investig Drugs. 2016;25(6):667-77.
14. Bockorny B1, Pectasides E. The emerging role of immunotherapy in gastric and esophageal adenocarcinoma. Future Oncol. 2016;12(15):1833-46.
15. Muro K, Chung HC, Shankaran V, Geva R, Catenacci D, Gupta S, Eder JP, Golan T, Le DT, Burtness B, McRee AJ, Lin CC, Pathiraja K, Lunceford J, Emancipator K, Juco J, Koshiji M, Bang YJ. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. Lancet Oncol. 2016;17(6):717-26.
16. Le DT, Bendell JC, Calvo E, Kim JW, Ascierto PA, Sharma P, Ott PA, Bono P, Jaeger D, Evans TRJ, De Braud FG, Chau I, Christensen O, Harbison C, Lin C-S, Janjigian YY. Safety and activity of nivolumab monotherapy in advanced and metastatic (A/M) gastric or gastroesophageal junction cancer (GC/GEC): Results from the CheckMate-032 study. J Clin Oncol. 2016; 34:(suppl 4S; abstr 6).
17. Janjigian YY, Bendell JC, Calvo E, Kim JW, Ascierto PA, Sharma P, Ott PA, Bono P, Jaeger D, Evans TRE, De Braud FG, Chau I, Tschaika M, Harbison CT, Chen-Lin S, Le DT. CheckMate-032: Phase I/II, open-label study of safety and activity of nivolumab (nivo) alone or with ipilimumab (ipi) in advanced and metastatic (A/M) gastric cancer (GC). J Clin Oncol.2016;34:(suppl; abstr 4010).
18. Kang Y-K, Satoh T, Ryu M-H, Chao Y, Kato K, Chung HC, Chen J-S, Muro K, Kang WK, Yoshikawa T, Oh SC, Tamura T, Lee-W, Boku N, Chen L-Z. Nivolumab (ONO-4538/BMS-936558) as salvage treatment after second or later-line chemotherapy for advanced gastric or gastro-esophageal junction cancer (AGC): A double-blinded, randomized, phase III trial. J Clin Oncol. 2017;35:(suppl 4S; abstract 2).
19. Janjigian YY, Adenis A, Aucoin J-S, Barone C, Boku N, Chau I, Cleary JM, Kynan Feeney, Franke FA, Moehler M, Roca EL, Schenker M, Li M, Ajan JA. Checkmate 649: A randomized, multicenter, open-label, phase 3 study of nivolumab (Nivo) plus ipilimumab (Ipi) versus oxaliplatin plus fluoropyrimidine in patients (Pts) with previously untreated advanced or metastatic gastric (G) or gastroesophageal junction (GEJ) cancer. J Clin Oncol. 2017;35:(suppl 4S; abstract TPS213).
20. Weichselbaum RR, Liang H, Deng L, Fu YX. Radiotherapy and immunotherapy: a beneficial liaison? Nat Rev Clin Oncol. 2017;17. doi: 10.1038/nrclinonc.2016.211.
21. Ng J, Dai T. Radiation therapy and the abscopal effect: a concept comes of age. Ann Transl Med. 2016;4(6):118. doi: 10.21037/atm.2016.01.32.
22. Jackie Oh S, Han S, Lee W, Lockhart AC. Emerging immunotherapy for the treatment of esophageal cancer. Expert Opin Investig Drugs. 2016;25(6):667-77.
23. Sahin U, Koslowski M, Dhaene K, Usener D, Brandenburg G, Seitz G, Huber C, Türeci O. Claudin-18 splice variant 2 is a pan-cancer target suitable for therapeutic antibody development. Clin Cancer Res. 2008; 14(23): 7624-34.
24. Al-Batran S-E, Schuler MH, Zvirbule Z, Manikhas G, Lordick F, Rusyn A, Vynnyk Y, Vynnychenko I, Fadeeva N, Nechaeva M, Dudov A, Gotovkin E, Pecheniy A, Bazin I, Bondarenko I, Melichar B, Mueller C, Huber C, Tureci O, Sahin U. FAST: An international, multicenter, randomized, phase II trial of epirubicin, oxaliplatin, and capecitabine (EOX) with or without IMAB362, a first-in-class anti-CLDN18.2 antibody, as first-line therapy in patients with advanced CLDN18.2+ gastric and gastroesophageal junction (GEJ) adenocarcinoma. J Clin Oncol. 2016;34:(suppl; abstr LBA4001).
25. Hoss A. Evolution of end points for cancer immunotherapy trials. Ann Oncol. 2012;23 Suppl 8:viii47-52.
26. Moehler M, Delic M, Goepfert K, Aust D, Grabsch HI, Halama N, Heinrich B, Julie C, Lordick F, Lutz MP, Mauer M, Alsina Maqueda M, Schild H, Schimanski CC, Wagner AD, Roth A, Ducreux M. Immunotherapy in gastrointestinal cancer: Recent results, current studies and future perspectives. Eur J Cancer. 2016;59: 160-70.

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