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Does the use of radiation therapy combined with monoclonal antibodies against CTLA-4 increase endocrine toxicity?

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Η ακτινοθεραπεία σε συνδυασμό με μονοκλωνικά αντισώματα κατά του CTLA-4 αυξάνει την ενδοκρινική τοξικότητα;

Περίληψη στο τέλος του άρθρου

Key words: Endocrine toxicity, Monoclonal antibodies, Radiotherapy, T lymphocyte-associated antigen-4, Treatment

T cell activation is known to be an important factor in immunization against tumor cells. An effective T cell response can be achieved by the reaction between the receptor and its corresponding ligand in the antigen producing cell. The balance between the activator and inhibitor signals determines the activation level of the immune system. Promising, novel strategies against immune checkpoints have been developed in the management of cancer. Currently, T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death protein-1 (PD-1) and programmed cell death ligand (PDL-L1), which have an inhibitory effect on the immune system, are the immune checkpoints which have been most intensively investigated.[1–3]

CTLA-4 was the first immune checkpoint receptor to be studied. It is encoded by the chromosome *2q33* gene and expressed by active T lymphocytes. It is a negative regulator of T cell activation.[1,2] Genetic defects in the CTLA-4 molecule have been documented to cause fatal autoimmune and lymphoproliferative diseases in animal models.[4] It has been determined that dysfunction of the CTLA-4 antigen leads to various autoimmune disorders in humans, also, and in this context, *CTLA-4* gene polymorphism is associated with impaired control of T cell proliferation. Single nucleotide polymorphisms (SNPs) in the *CTLA-4* gene lead to systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Graves' disease, autoimmune hypothyroidism and celiac disease.[5] CTLA-4 49A/G polymorphism is associated with an increased risk of various solid tumors, including osteosarcoma and breast, bladder and colorectal cancer, due to weakening of the anti-tumor response. CTLA-4 activation is thought to increase the stimulation and activation threshold of T cells, suppress the antitumor response and increase cancer susceptibility.[1,6–8]

Identification of core receptors which prevent CTLA-4 T cell activation and allow avoidance of development of tumor cells dependent on the immune response led to the introduction of novel therapies targeting these mechanisms. Monoclonal antibodies developed against CTLA-4 inhibit the binding of CTLA-4 to the ligand, and thus increase T cell proliferation and enhance the immune response to the tumor. I ipilimumab, a monoclonal antibody developed against CTLA-4, has been used clinically in patients with advanced stage melanoma, and phase II and III studies on the effectiveness and toxicity of this agent are ongoing. It has been reported that the most important side effect of I ipilimumab is autoimmunity.[1,2,6–8] Dewan and colleagues, in a rat study, showed that the combination of CTLA-4 blockade with radiotherapy improved the likelihood of systemic tumor control in tumors resistant to CTLA-4 blockade.[3] A recent review reported that anti-CTLA-4 agents caused thyroid dysfunction in 23% of patients, suggesting periodical monitoring of thyroid function on the start of immunotherapy.[1] The prevalence and mechanism of endocrine adverse events are unclear, and the authors

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emphasized the need for further studies to identify and confirm predictive factors for autoimmune toxicity.[2]

In conclusion, CTLA-4 is negative regulator of the T cells that play a critical role in the immune response against tumors. The prognostic and predictive significance of CTLA-4 in many tumor types continues to be the subject of research and debate. In adults, the endocrine system is rarely damaged by traditional cancer treatment, with the exception of the direct toxicity of radiotherapy. The monoclonal antibodies developed against CTLA-4 may also cause endocrine dysfunction, at a variable rate, and their concomitant use with radiotherapy may increase endocrine toxicity by additive action. It is important to investigate interaction between endocrine toxicity factors in the case of combined use of radiotherapy and the novel strategies directed against immune checkpoints in the treatment of cancer.

ΠΕΡΙΛΗΨΗ

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Η αποτελεσματική Τ-κυτταρική απόκριση μπορεί να επιτευχθεί μέσω της αλληλεπίδρασης υποδοχέα-συνδέτη στα αντιγονοπαρουσιαστικά κύτταρα. Υπάρχει μια ισορροπία ανάμεσα στα ενεργοποιητικά και στα ανασταλτικά σηματοδοτικά μονοπάτια του ανοσοποιητικού που καθορίζουν τον βαθμό ενεργοποίησής του. Επί του παρόντος, θεραπευτικές μέθοδοι κατά μονοπατιών του ανοσοποιητικού έχουν ενσωματωθεί σε νέες, πολλά υποσχόμενες στρατηγικές στην αντιμετώπιση του καρκίνου. Συγκεκριμένα, το σχετιζόμενο με τα Τ-λεμφοκύτταρα αντιγόνο-4 (T lymphocyte-associated antigen-4, CTLA-4) είναι το πλέον ευρέως χρησιμοποιούμενο μόριο-στόχος. Το CTLA-4 είναι αρνητικός ρυθμιστής των Τ-κυττάρων, το οποίο κατέχει σημαντικό ρόλο στην ανοσιακή απάντηση έναντι των όγκων. Η προγνωστική και προβλεπτική αξία των τιμών του CTLA-4 είναι αντικείμενο συζήτησης. Στους ενήλικες, με την εξαίρεση της άμεσης τοξικότητας της ακτινοβολίας, το ενδοκρινικό σύστημα απορρυθμίζεται σπάνια. Μονοκλωνικά αντισώματα κατά του CTLA-4 μπορεί να προκαλέσουν ενδοκρινική δυσλειτουργία ποικίλου βαθμού. Η χρήση μονοκλωνικών αντισωμάτων σε συνδυασμό με ακτινοβολία μπορεί να αυξήσει την τοξικότητα μέσω μηχανισμών αθροιστικής επίδρασης. Η κατανόηση της ισορροπίας ανάμεσα σε δυνητικά τοξικούς παράγοντες κατά τη χορήγηση συνδυασμένων θεραπειών είναι σημαντική, καθιστώντας επιτακτική την ανάγκη για περαιτέρω μελέτη αυτών.

Λέξεις ευρετηρίου: Ακτινοθεραπεία, Ενδοκρινική τοξικότητα, Θεραπεία, Μονοκλωνικά αντισώματα, CTLA-4, Τ-λεμφοκύτταρα αντιγόνο-4

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