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REVIEW ARTICLE

Agnieszka Chmielewska[1], Tomasz Kubiatowski[1, 2]

[1]"Rafal Masztak, MD PhD" Grochowski Hospital in Warsaw [sp. z o.o.], Poland
[2]Department of Oncology, University of Warmia Mazury in Olsztyn, Poland

Role of TROP 2 overexpression in selected solid tumors

Address for correspondence:
Agnieszka Chmielewska, MD
"Rafal Masztak, MD PhD" Grochowski Hospital in Warsaw [sp. z o.o.]
ul. Grenadierów 51/59,
04–073 Warsaw, Poland
e-mail: achmielewska@grochowski.waw.pl

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ABSTRACT

Cancer cell research development has led to the identification of many cell-surface proteins and signaling pathways that are required for cancer cell proliferation. TROP2 is one of the cell-surface proteins expressed in normal tissues. However, its overexpression is present in many types of malignant tumors. TROP2 overexpression may be a prognostic factor and a foothold for targeted therapies. Treatment with antibody-drug conjugates is applied in systemic cancer therapy. Currently, clinical trials are underway to evaluate the efficacy and safety of TROP2-targeted therapies.

Keywords: TROP 2 protein, targeted therapy, antibody-drug conjugate

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Introduction

Trophoblast-cell surface antigen 2 (TROP2) receptor protein — also referred to as GA733-1 (gastrointestinal antigen 733-1), EGP-1 (epithelial glycoprotein-1), TACSTD2 (tumor-associated calcium signal transducer- 2) — is a transmembrane glycoprotein with a molecular weight of 36 kDa, which was initially discovered on both normal and neoplastic trophoblast cells [1, 2]. TROP2 is a protein product of the TACSTD2 gene located on chromosome 1p32, which acts as a cellular proto-oncogene. Its mutation leads to the acquisition of an oncogenic function, which determines the transformation process of the primary cancer cells and their ability to metastasize. The TROP2 protein is synthesized in the endoplasmic reticulum, and then it is transported to the Golgi apparatus, where its glycosylation takes place. Its expression is found on the surface of the cell membrane and within the cytoplasm, with the presence of membrane expression associated with — unlike the cytoplasmic location — worse clinical prognosis manifested by an increased percentage of disease recurrences [3].

The question of causes of TROP2 protein overexpression in cancer cells remains open. It is thought that some transcription factors [e.g. Wilm's tumor 1 (WT1)] involved in progression of cancer are also factors regulating TROP2 transcription [4].

TROP2 overexpression in cancer cells, having prognostic significance, makes the protein a potential candidate for targeted therapies. The meta-analysis by Zeng et al. [5], published in 2016, showed, in a group of over 2500 patients with solid tumors, a relationship between TROP2 protein overexpression and shortened overall survival (OS) and disease-free survival (DFS).

The following article summarizes the data in the literature on changes in the expression of the TROP2 protein on the surface of cells of selected cancers and discusses its clinical implications and possible directions for the development of targeted therapies.

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Cervical cancer

Analyzing the expression of the TROP2 protein in cervical cells, Liu et al. [6] showed a relationship between its expression found immunohistochemically in 89% of the examined preparations and the stage of the neoplastic process according to the The International Federation of Gynecology and Obstetrics (FIGO) classification, the degree of histological differentiation, depth infiltration, the presence of metastases in the lymph nodes, and the expression of Ki67. The authors showed that patients with TROP2 overexpression were characterized by shorter progression-free survival (PFS) and OS. Overexpression of the TROP2 protein significantly stimulated the proliferation of cervical cancer cells and was closely related to the activation of stromal cell infiltration in the tumor. Reduced expression of TROP2 increased the sensitivity of tumor cells to the effects of platinum derivatives.

Endometrial cancer

In patients diagnosed with endometrial cancer, TROP2 overexpression in conjunction with FIGO staging is an independent factor of poor prognosis. In the study by Bignotti et al. [7], overexpression of TROP2 correlated with a lower grade of tumor differentiation ($p = 0.02$), shortened DFS ($p = 0.01$), PFS ($p = 0.05$), and OS ($p = 0.06$).

Ovarian cancer

High expression of TROP2 was demonstrated in 83% of ovarian cancer cell lines based on quantitative real-time polymerase chain reaction (qRT-PCR) and flow cytometry [8]. Overexpression of TROP2 correlates with a more aggressive clinical course of ovarian cancer and resistance to chemotherapy. In studies evaluating the importance of TROP2 in ovarian cancer, it was confirmed that the reduction of TROP2 expression inhibits the proliferation of cancer cells and reduces their metastatic capacity [9].

Central nervous system tumors

Central nervous system (CNS) glial tumors clearly overexpress the TROP2 protein, which is not found in normal tissues. The lower the tumor grade (WHO III and WHO IV gliomas), the greater the degree of TROP2 expression. The relationship between TROP2 expression and sex or age of patients has not been determined [10].

Colorectal cancer

TROP2 expression in colorectal cancer cells is clearly higher than in normal cells and is associated with worse prognosis, increased risk of recurrence, and metastases in the liver [11]. TROP2 overexpression is found more frequently in tumors involving the left side of the intestine (67.5% *vs.* 32.5%; $p = 0.002$). Mortality associated with colorectal cancer is four times higher in patients with high TROP2 expression (40% *vs.* 10%; $p = 0.002$). Patients with left-sided colorectal cancer and high expression of TROP2 have shorter median OS (45.9 *vs.* 63.1 months, $p = 0.032$) compared to those with low expression. In the case of cancers of the right half of the large intestine, TROP2 expression has no clear effect on survival ($p = 0.235$).

Gastric cancer

TROP2 expression is an independent risk factor for disease recurrence, which is particularly true for intestinal gastric cancer, regardless of the degree of regional lymph node involvement caused by the neoplastic process [12]. Finding overexpression of TROP2 is associated with shorter DFS ($p = 0.03$). In a study by Farivar et al. [13], it was shown that the TROP2 protein is a potential candidate for targeted therapy. The use of modified liposomes, which are a "transporter" for apoptosis activator 2, and then their introduction into gastric adenocarcinoma cell lines with overexpression of TROP2, allowed determining the activation of the apoptosis process in a greater percentage of the analyzed cells.

Esophageal cancer

In a study by Nakashima et al. [14], the presence of antibodies against TROP2 in the serum of patients diagnosed with squamous cell carcinoma of the esophagus was analyzed. The presence of anti-TROP2 antibodies found in 31% of patients correlated with the size of the primary tumor. The association of anti-TROP2 antibody presence with other clinical features has not been confirmed. The analysis of pathomorphological features showed a significantly higher expression of the TROP2 protein on the surface of cancer cells compared to hyperplastic lesions of the esophageal mucosa.

Cholangiocarcinoma

In the case of cholangiocarcinoma (CCA), the expression of TROP2 on cancer cells is significantly higher than that shown in normal tissue ($p = 0.001$). The

analysis of data from the study by Ning et al. [15] showed a relationship between the expression of TROP2, the degree of histological differentiation of the tumor ($p = 0.016$), and the size of the tumor (T feature $p = 0.031$). Patients diagnosed with cholangiocarcinoma with high expression of TROP2 are characterized by shorter OS compared to those with low expression of the TROP2 receptor protein. TROP2 expression in CCA is considered to be an independent prognostic factor.

Pancreatic cancer

TROP2 expression is clearly higher in pancreatic cancer cells compared to peritumoral tissues (87.1% *vs.* 9.7%) [16]. High expression of TROP2 is associated with a low degree of tumor differentiation and is not dependent on sex or age of the patient.

Oral cavity cancer

TROP2 overexpression in the study by Fong et al. [17] in patients diagnosed with squamous cell carcinoma of the oral cavity was associated with shortened OS ($p < 0.01$), with the relationship being inversely proportional to the degree of overexpression of the receptor protein. Therefore, similar to other cancers, finding TROP2 overexpression in oral cavity squamous cell carcinoma cells is considered an independent prognostic factor associated with poor prognosis.

Lung cancer

TROP2 overexpression is more common in squamous cell lung cancer than in adenocarcinoma ($p < 0.01$) and is related to the degree of histological differentiation [18]. It seems that the role of TROP2 varies depending on the histological type of lung cancer. In the study by Inamura et al. [19], overexpression of TROP2 on adenocarcinoma cells was associated with shortened OS, while no similar relationship was observed in squamous cell carcinoma. Also, in the case of patients diagnosed with small cell lung cancer, high TROP2 expression did not affect survival time.

The effect of using an antibody combined with a cytotoxic drug (sacituzumab govitecan) in subsequent lines of treatment in patients with advanced non-small cell lung cancer (NSCLC) was assessed in a single-arm phase II study [20]. The study included 54 patients who received from two to seven lines of systemic therapy in the earlier stages of treatment. The objective response rate (ORR) was 19%, and the mean duration of response to treatment was 6 months (range 4.8–8.3 months). The clinical benefit rate (sum of complete and partial responses plus disease stabilization for more than 4 months) was 43%. Median PFS and OS were 5.2 months (range 3.2–7.1 months) and 9.5 months, respectively. Treatment was well tolerated, grade 3 and higher toxicities included neutropenia (28%), diarrhea (7%), nausea (7%), fatigue (6%), and febrile neutropenia (4%). Based on the conducted analyses, it can be concluded that the use of sacituzumab govitecan in this group of patients led to obtaining, with acceptable toxicity, long-term responses in patients with metastatic NSCLC in subsequent lines of treatment.

The clinical effect and toxicity resulting from the use of sacituzumab govitecan in patients with advanced small cell lung cancer (SCLC) was evaluated in a phase II study [21]. Clinical benefit from treatment, defined similar to that of the previous study, was reported by 34% of the subjects. Median OS was 7.5 months and median PFS was 3.7 months. Treatment was well tolerated, grade 3 and higher toxicities included anemia (6%), diarrhea (9%), and fatigue (13%), with the most commonly observed being neutropenia (34%). In the study, no significant differences were observed in the response to treatment with sacituzumab govitecan in the groups of patients sensitive and resistant to first-line treatment.

Work on anti-TROP2 antibodies and conjugates of antibodies with cytotoxic drugs allowed the creation of another molecule, which is datopotamab deruxtecan (Dato-Dxd; DS-1062), which is a conjugate of a humanized monoclonal anti-TROP2 class IgG1 with topoisomerase type inhibitor I. Preclinical studies confirmed the in vitro activity of the drug in cells expressing TROP2 [22]. In the TROPION-PanTumor01 study [23], 133 patients diagnosed with relapsed NSCLC received at least 1 cycle of treatment (81% — prior immunotherapy, 90% — prior platinum-based chemotherapy). According to the results of the preliminary analysis, the ORR was 79% at a dose of 4 mg/kg and 75% and 79% in patients receiving the study drug at a dose of 6 mg/kg and 8 mg/kg, respectively. Most of the patients experienced adverse effects of treatment of varying severity (96%), with nausea (50%), stomatitis (44%), alopecia (40%), and increased fatigue (48%) being the most common.

Breast cancer

The expression of the TROP2 receptor protein on ductal breast cancer cells is significantly higher than in normal tissues and correlates with the degree of histological differentiation ($p = 0.023$) and the presence of metastases in regional lymph nodes ($p < 0.01$) and distant metastases ($p = 0.04$) [24]. High expression of TROP2 and the presence of metastases in lymph nodes

are independent prognostic factors and are associated with worse prognosis in the case of ductal breast cancer. The level of TROP2 expression is closely related to the cancer subtype and is higher in triple-negative breast cancer (TNBC) and luminal HER2-negative breast cancer cells compared to HER2-positive breast cancer cells [25, 26].

In studies of breast cancer conducted on mouse models, it was found that fragments binding the TROP2 antigen (TROP2-Fab, TROP2 antigen-binding fragment) have an inhibitory effect on tumor cell proliferation and activation of the apoptosis process as a result of stimulating the expression of caspase 3 and inhibiting the function of the bcl2 protein [27]. The findings led to the creation of an anti-TROP2 antibody conjugate with a cytotoxic drug. Sacituzumab govitecan is a combination of anti-TROP2 antibody with SN-38, which is the active metabolite of irinotecan. Goldenber et al. [28] confirmed in their studies that the use of govitecan sacituzumab allows for a much higher concentration of irinotecan in mouse breast cancer cells with lower toxicity of the treatment. In the phase I-II basket study, involving 25 patients with confirmed malignant disease with varying primary tumor locations, the use of sacituzumab govitecan allowed 3 out of 4 patients with metastatic TNBC to achieve a partial response to treatment — with a duration of 10.4 months, 6.9 months, and 3.1 months, respectively [29].

In another single-arm phase I–II study, the efficacy of govitecan sacituzumab was assessed in a group of 108 patients with disseminated TNBC who progressed despite the use of subsequent lines of chemotherapy [30]. The ORR rate was 33.3% (including complete remission in 3 patients). The median duration of response was 8.9 months (range 6.1–11.3 months). The treatment was well tolerated, and the most common grade 3 and higher adverse events were mainly hematological complications (neutropenia — 26%, anemia — 11%, and diarrhea — 8%). Diarrhea in lower toxicity grades affected 62% of patients. The results of the study confirmed that treatment with sacituzumab govitecan leads to a rapid and durable response in patients with TNBC previously having undergone systemic treatment of subsequent lines.

The results of the presented analyses made it possible to plan the first phase III study — ASCENT study [31]. It included 468 patients diagnosed with metastatic TNBC following at least two systemic treatments. The efficacy of treatment with sacituzumab govitecan was compared to what was observed in the chemotherapy arm of the study (eribulin, vinorelbine, capecitabine, or gemcitabine). The use of anti-TROP2 conjugated to the active metabolite of irinotecan led to an improvement in median PFS of 3.9 months compared to chemotherapy alone (5.6 *vs.* 1.7 months, risk reduction of 59%, $p < 0.001$), median OS of 5.4 months (12.1 *vs.* 6.7 months, 52% risk reduction, $p < 0.001$). The duration of response with sacituzumab govitecan and chemotherapy alone was 6.3 months and 3.6 months, respectively (61% risk reduction). Treatment with sacituzumab govitecan was fairly well tolerated, and only 5% of patients in the experimental arm discontinued treatment due to intolerable toxicity.

The clinical effect and safety of sacituzumab govitecan were also assessed in a group of 50 patients with early TNBC (NeoSTAR study) [32]. According to the study protocol, the patients received 4 cycles of treatment, followed by a biopsy of the lesion and, if the presence of neoplastic cells was found, chemotherapy treatment was continued. Pathologic complete response (pCR) was achieved in 30% of patients.

There are currently many studies evaluating the clinical effect of combining sacituzumab govitecan with other drugs in patients with TNBC (e.g. phase II randomized study Saci-IO = NCT04468061 — in combination with pembrolizumab in the first-line treatment of metastatic TNBC).

Clinical trials are also conducted using anti-TROP2 antibody conjugates with cytotoxic drugs in breast cancer subtypes other than TNBC. In a study by Kalinsky et al. [33], the efficacy of treatment with sacituzumab govitecan was assessed in a group of 54 patients with metastatic hormone-sensitive and HER2-negative breast cancer who experienced disease progression during hormonal treatment and received at least one line of chemotherapy treatment. With a median follow-up of 11.5 months, the ORR was 31.5%, and median PFS and OS were 5.5 and 12 months, respectively.

The preliminary results of the studies were confirmed in the phase III study TROPICS-02, which assessed the efficacy of treatment with sacituzumab govitecan [34]. The study included 543 patients diagnosed with disseminated luminal B carcinoma with HER2(–) feature, who had previously received two to four lines of treatment, including hormone therapy, CDK4/6 inhibitor, and taxane-based chemotherapy. Patients were randomized 1:1 to either the experimental arm (sacituzumab govitecan) or the control arm (chemotherapy of investigator's choice — eribulin, vinorelbine, capecitabine, or gemcitabine). The results of the interim analysis showed that the use of sacituzumab govitecan led to a statistically significant prolongation of PFS compared to patients undergoing chemotherapy (5.5 *vs.* 4.0 months — risk reduction by 44%, $p = 0.0003$). A subsequent analysis (median follow-up 12.5 months) showed prolonged OS compared to chemotherapy (median 14.4 *vs.* 11.2 months, risk reduction of 21%, $p = 0.020$).

Data on the use of Dato-Dxd in treatment of patients with disseminated TNBC following failure of previous therapies were presented in the form of congress reports presented during the SABCS (San

Antonio Breast Cancer Symposium) [35]. The study involved 44 patients with disseminated TNBC after an average of three lines of treatment for advanced disease. CNS metastases were found in 11% of patients. The ORR was 32% and the median duration of response to presentation time was not reached. Grade 3 or higher treatment-related adverse events were observed in 45% of patients included in the treatment, with nausea (66%) and stomatitis (55%) being the most common. Neutropenia, anemia, and diarrhea have been observed less frequently than with sacituzumab govitecan.

Further studies are aimed at evaluating the clinical efficacy and safety of using Dato-Dxd in previous lines of treatment or in combination with other drugs. To date, the preliminary results of the BEGONIA study evaluating the therapeutic effect of the combination of Dato-Dxd with durvalumab in the first-line treatment of patients with generalized TNBC have been presented [36]. In the group of 27 patients evaluated thus far, a 74% ORR was obtained, regardless of PD-L1 expression.

Urothelial cancers

TROP2 protein is overexpressed on the surface of cancer cells in 80% of patients with urothelial carcinoma. The prognostic significance of TROP2 overexpression in this tumor has not been confirmed, however, the presence of TROP2 protein may be a candidate for targeted therapies. In a phase I-II study by Faltas et al. [37], the efficacy of sacituzumab govitecan was assessed in a group of 6 patients diagnosed with advanced urothelial carcinoma following an average of three lines of previous treatment. In 3 patients, response to treatment was achieved, PFS was between 6.7 and 8.2 months, depending on the patient, and OS was between 7.5 and 11.4 months. The treatment was well tolerated.

Prostate cancer

Research conducted in prostate cancer confirmed the role of TROP2 protein in regulating the function of integrin b1, which affects the ability of cancer cells to form metastases. TROP2 also affects the activity of GTPase Rac1 and consequently the induction of the activity of the PAK4 protein, which increases the ability of prostate cancer cells to migrate and form distant metastases. The study by Trerotola et al. [38] demonstrated the regulatory effect of TROP2 on the adhesion of prostate cancer cells to fibronectin through the signaling pathway mediated by integrin b1, -RACK1, -Src- and FAK proteins, which is essential for the ability of cancer cells to migrate and metastasize.

Conclusions

TROP2 expression is present in normal and neoplastic cells. Overexpression of the TROP2 protein is a prognostic factor in many cancers and a candidate for targeted therapies. Therapy using anti-TROP2 antibody conjugates with a cytotoxic drug is applicable in the treatment of patients with multiple solid tumors. The presence of the TROP2 protein in normal cells does not lead to a significant increase in the toxicity of the treatment, which is most likely due to the stronger relationship between the toxicity and the cytotoxic drug contained in the conjugations. The results of many studies that confirm the efficacy of anti-TROP2 treatment are already available. The results of further studies evaluating the clinical effect and safety of anti-TROP2 antibody conjugates with a cytotoxic drug in monotherapy and in combination with other molecules are awaited with great interest.

Article Information and Declarations

Author contributions

A.C., T.K.: contributed equally in the preparation of the manuscript.

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Conflict of interest

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