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Impact of IMP3 Expression on Chemotherapy Response and Prognosis in Triple-Negative Breast Cancer: A Retrospective Cohort Study

Mio Yagi[1], Koji Nagata[2], Megumi Sano[1],
Keiko Yanagihara[1], Ryuji Ohashi[3] and Hiroyuki Takei[4]

[1]Department of Breast Surgery and Oncology, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan
[2]Department of Diagnostic Pathology, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan
[3]Department of Integrated Diagnostic Pathology, Nippon Medical School, Tokyo, Japan
[4]Department of Breast Surgery and Oncology, Nippon Medical School Hospital, Tokyo, Japan

Background: Although advances in neoadjuvant chemotherapy (NAC) are improving the rate of pathological complete response (pCR) and outcomes for triple-negative breast cancer (TNBC) patients, the prognosis remains poor. Insulin-like growth factor II mRNA-binding protein 3 (IMP3) expression was recently reported to be associated with chemotherapy resistance and poor prognosis in TNBC.
Methods: We evaluated IMP3 expression in 40 female TNBC patients to assess its association with NAC sensitivity and outcome.
Results: Among the cohort, 11 patients (27.5%) had IMP3-positive TNBC, which was associated with a higher Ki-67 labeling index ($p = 0.119$), indicating greater malignancy. However, IMP3 positivity showed no significant correlation with NAC resistance or differences in disease-free survival (DFS) as compared with IMP3-negative patients.
Conclusions: Patients receiving effective immunotherapy or high-dose chemotherapy achieved pCR regardless of IMP3 status, which suggests that the NAC regimen is more important than IMP3 status for pCR. Even in IMP3-positive TNBC, NAC may improve prognosis by achieving pCR. Thus, while IMP3 might predict poor prognosis, it may not serve as a definitive marker in the context of NAC. Because IMP3 is involved in cancer stem cell (CSC) function, further research is necessary to understand its complex role in CSCs and TNBC. (J Nippon Med Sch 2025; 92: 44–51)

Key words: triple-negative breast cancer, neoadjuvant chemotherapy, IMP3, pathological complete response, prognosis

Introduction

Breast cancer is the most common cancer in women: 1 of 9 women receives a diagnosis of breast cancer in their lifetime[1]. In Japan, most women with breast cancer are diagnosed between 40 and 60 years of age. Breast cancer strikes at a young age and can be fatal. Furthermore, in patients with triple-negative breast cancer (TNBC), which accounts for approximately 15% of all breast cancers, hormone and anti-epidermal growth factor receptor 2 (HER2) therapies are ineffective and prognosis is generally poor[2,3]. The effectiveness of chemotherapy is often limited, and outcomes are sometimes poor.

Previous studies reported that increased expression of insulin-like growth factor II mRNA-binding protein 3 (IMP3) is associated with aggressive tumor behavior, advanced clinical stage, distant metastasis, and shorter overall survival[4–6]. Ki-67 is a protein involved in cell proliferation and is an indicator of the extent of cell division and proliferation. Cells actively undergoing proliferation exhibit increased Ki-67 expression, which is an important marker of cancer activity and prognosis. Thus, we also examined the association between IMP3 and Ki-67 ex-

Correspondence to Mio Yagi, Department of Breast Surgery and Oncology, Nippon Medical School Tama Nagayama Hospital, 1–7–1 Nagayama, Tama, Tokyo 206–0021, Japan
E-mail: m-yagi@nms.ac.jp
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pression, as indicated by the Ki-67 labeling index. In a previous study, TNBC cells expressing the oncofetal protein IMP3, as determined with immunohistochemistry, were resistant to neoadjuvant chemotherapy (NAC), and patients had poor outcomes[6]. However, with recent remarkable advances in TNBC treatment, prognosis can be favorable in patients who achieve pathologic complete response (pCR) with NAC[7]. Dose-dense therapy[8–10] and cancer immunotherapy[11], which have recently been introduced in clinical practice, are expected to improve pCR rates and prognosis. Although IMP3 expression is associated with poor outcomes for multiple cancer types[12–16], no study to date has evaluated the association between IMP3 expression in breast cancer and sensitivity to recent chemotherapy regimens. Therefore, the present study evaluated the association of IMP3 expression in TNBC with sensitivity to chemotherapy and disease-free survival (DFS).

Materials and Methods

Case Selection

In the present study, all women who underwent breast biopsy or surgery for the diagnosis and treatment of breast disease in the study center between January 1, 2020, and December 31, 2023, were evaluated and included if they (1) had received a diagnosis of clinical stage I-IV breast cancer, (2) had received a pathologic diagnosis of invasive ductal carcinoma or invasive lobular carcinoma, a special type, based on needle biopsy, with triple negativity for estrogen receptor (ER), progesterone receptor (PgR), and HER2, and (3) had undergone observation only or received treatment, including surgery and chemotherapy. Diagnosis of TNBC was based on ER and PgR negativity, defined as the presence of <1% ER-positive and PgR-positive cells by immunohistochemistry, respectively, and HER2 negativity, defined as a score 0 or 1+ by immunohistochemistry or a score of 2+ by immunohistochemistry with negative *HER2* by *in situ* hybridization. In the present study, patients received chemotherapy for at least 4 weeks before or after surgery. The regimens included (1) epirubicin and cyclophosphamide with a taxane, (2) pembrolizumab, carboplatin, and paclitaxel, and (3) bevacizumab and paclitaxel.

Pathologic Evaluation and Immunohistochemical Staining

Pathologic evaluation and immunohistochemical staining were performed using pretreatment biopsy and surgical tissue samples. In the present study, pCR was defined as the absence of invasive cancer cells in a histopathologic evaluation. Additionally, morphologic analyses were conducted to determine tumor size, lymph node metastasis, histologic type, and histologic grade.

Immunohistochemical staining was performed to assess associations between the Ki-67 labeling index, percentage of ER-positive cells, percentage of PgR-positive cells, HER2 score, and IMP3 expression. IMP3 expression was determined in needle-biopsy and surgical specimens. Immunohistochemical staining was performed using the standard avidin-biotin-peroxidase complex technique in samples prepared from formalin-fixed paraffin embedded tissue blocks. The following primary antibodies were used: mouse monoclonal anti-human IMP3 (M3626, 1:200; Dako, Denmark), rabbit monoclonal anti-human ER (SP1, 1:1; Ventana Medical Systems, Tucson, AZ, USA), rabbit monoclonal anti-human PgR (1E2, 1:1; Ventana Medical Systems), rabbit monoclonal anti-human HER2/Neu (4B5, 1:1; Ventana Medical Systems), and mouse monoclonal anti-human Ki-67 (M7240, 1:100; Dako, Denmark). Positive and negative controls were included for each antibody. IMP3-positive staining was defined as brown staining of the cytoplasm or cell membrane. IMP3 expression in tumor cells was evaluated using the Allred score, as follows: total score = proportion score (PS) + intensity score (IS). The PS was assigned as follows: No staining = 0, <1% of nuclear staining = 1, 1-10% of nuclear staining = 2, 11-33% of nuclear staining = 3, 34-66% of nuclear staining = 4, and 67-100% of nuclear staining = 5. The IS was assigned as weak = 1, intermediate = 2, and strong = 3. Tumor samples with a total score of ≥3 were defined as positive for IMP3 expression (**Fig. 1**).

Types of Chemotherapy for Patients with TNBC

In patients with stage I-III breast cancer, anthracycline and taxane are commonly used as NAC, which is typically administered every 2-3 weeks. Discussions regarding biweekly administration began in the early 2000s[17], with the more effective biweekly administration becoming common clinical practice around 2020.

In the present study cohort, epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) were administered, followed by paclitaxel (175 mg/m^2). All drugs were given every 2 weeks for a total of 4 cycles each (dose-dense therapy). The dosing schedule aimed to shrink tumors before surgery by more frequent administration and to reduce the risk of cancer recurrence. However, because biweekly administration can increase the rate of adverse events[9,10,18], elderly patients and those with underlying medical conditions received epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2), followed by docetaxel

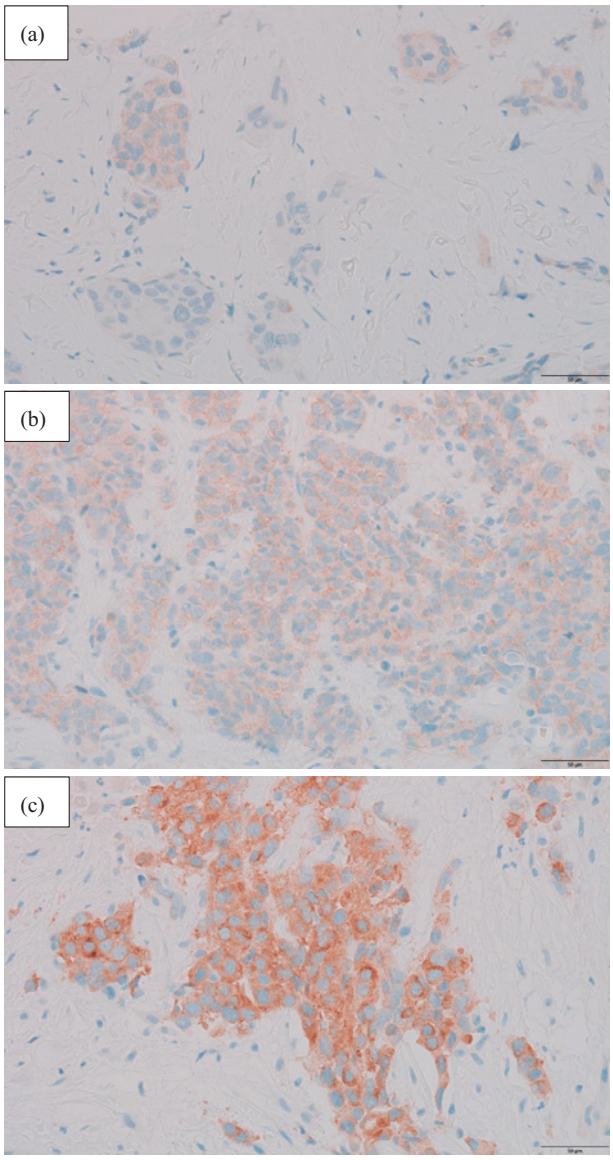


Fig. 1 Images of IMP3 staining intensity in TNBC Tumors
Representative images of tumor samples illustrating IMP3 staining (brown) intensities of 1+ (a), 2+ (b), and 3+ (c). IMP3 expression in tumor cells was evaluated using the Allred score. A total score of ≥3 indicates IMP3 positivity, whereas a total score of <3 indicates IMP3 negativity.

(75 mg/m^2), which were administered every 3 weeks for a total of 4 cycles each.

In April 2022, the immune checkpoint inhibitor (ICI) pembrolizumab, which prevents the ability of tumor cells to evade the immune system and enhances the ability of the immune system to attack the tumor[19], became eligible for insurance coverage in Japan. Pembrolizumab is used as an NAC option for TNBC, for which hormone therapy and HER2-targeted therapy are not effective, opening new avenues in the treatment of this refractory cancer[11]. In patients who received pembrolizumab, carboplatin, and paclitaxel, the treatment regimen included pembrolizumab (200 mg/body) administered on day 1; paclitaxel (80 mg/m^2) on days 1, 8, and 15; and carboplatin (AUC 5) on day 1. The regimen was repeated every 3 weeks for 4 cycles. Subsequently, pembrolizumab (200 mg/body) was administered in combination with epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks for 4 cycles.

In patients with metastatic or locally advanced breast cancer, the combination of bevacizumab and paclitaxel may be used to reduce tumor size and increase the indications for surgery[20]. In the present study, patients received various treatments, including anthracyclines and taxanes, which were administered every 2-3 weeks, ICIs including pembrolizumab, and bevacizumab plus paclitaxel.

Statistical Analysis

The association of IMP3 expression with clinicopathologic factors and treatment response to chemotherapy were assessed. All statistical analyses were conducted using SPSS (version 29; IBM, Armonk, NY, USA), and a p value of <0.05 was considered statistically significant.

Institutional Review Board Statement

Consent for the use of clinical samples for research purposes was obtained from all patients, in accordance with the regulations defined by the Ethics Committee of Nippon Medical School Tama Nagayama Hospital (approval number: F-2023-082; January 22, 2024).

Results

Cohort Characteristics

The study cohort included 40 women, including 9, 17, 4, 1, 2, 5, and 2 patients with cStage I, IIA, IIB, IIIA, IIIB, IIIC, and IV breast cancer, respectively. The patient age ranged from 40 to 91 (median, 69.5) years. The observation period varied between 32 and 1,302 (median, 667) days. In the overall cohort, 5 patients had a history of previous breast cancer surgery and experienced locoregional recurrence (**Table 1**).

Efficacy of NAC in Relation to IMP3 Status

Eighteen patients received NAC, although treatment was stopped for 1 patient who could no longer tolerate it. Dose-dense therapy was administered to 10 patients, 3 patients who received anthracycline and taxanes every 3 weeks, 3 patients who received ICI therapy, and 2 patients who received bevacizumab plus paclitaxel.

A comparison of NAC efficacy in relation to IMP3 status revealed that 3 of the 10 patients treated with

Table 1 Clinical characteristics of patients with breast cancer, by IMP3 status

Variable	IMP3-positive (number = 11)	IMP3-negative (number = 29)	Total (number = 40)
Age (years)			
median	53	71	69.5
Range	40 - 81	41 - 91	40 - 91
Tumor size (mm)			
median	27	23	25.5
Range	17 - 100	5 - 100	5 - 100
Ki67 (%)			
median	48	33	39
Range	31 - 60	6 - 94	6 - 94
Nuclear Grade = 1	3	9	12
2	2	7	9
3	6	13	19
Histological Grade = 1	0	5	5
2	6	14	20
3	5	10	15
Lymph node status			
negative	5	20	25
positive	6	9	15
Clinical Stage 1	1	8	9
2	7	14	21
3	3	5	8
4	0	2	2
NAC			
Dose-dense therapy	3	7	10
ICI therapy	2	1	3
Anthracycline and taxanes every 3 weeks	2	1	3
Bevacizumab + paclitaxel	0	2	2
none	4	18	22

dose-dense therapy had IMP3-positive TNBC, including 2 patients who achieved pCR. The other 7 patients treated with dose-dense therapy had IMP3-negative TNBC, including 4 patients who achieved pCR. Additionally, pCR was not achieved in any of the 3 patients receiving chemotherapy every 3 weeks, including 2 patients with IMP3-positive TNBC and 1 patient with IMP3-negative TNBC. ICI therapy was administered to 3 patients, including 2 with IMP3-positive TNBC and 1 with IMP3-negative TNBC; all 3 patients achieved pCR. Both patients treated with bevacizumab were elderly women with bleeding, IMP3-negative TNBC; one received best supportive care because of overall deterioration after initial administration, and the other exhibited partial response to treatment.

Association of IMP3 Status with Pathologic Tumor Features

First, we examined the correlation between IMP3 expression and tumor size. The median tumor diameter was 27 mm for IMP3-positive patients and 23 mm for IMP3-negative patients, and no correlation was observed ($p = 0.42$). Among the overall cohort of 40 patients, 11 (27.5%) had IMP3-positive TNBC. One of the 5 patients with recurrence within the breast had IMP3-positive TNBC. Regardless of the results of the IMP3 staining, there was a tendency for high histologic and nuclear grades. Among the 18 patients who received NAC, 1 could not undergo surgery because of her poor general condition. Among the remaining 17 who received NAC, 7 had IMP3-positive TNBC, including 4, 2, and 1 patient who achieved pCR, near-pCR, and limited response, respectively. Among the 10 patients with IMP3-negative TNBC, 5, 2, and 3 patients achieved pCR, near-pCR, and limited response, respectively. In other words, among the 7 patients that were IMP3-positive, 4 (57.1%) achieved pCR, whereas among the 10 patients that were IMP3-

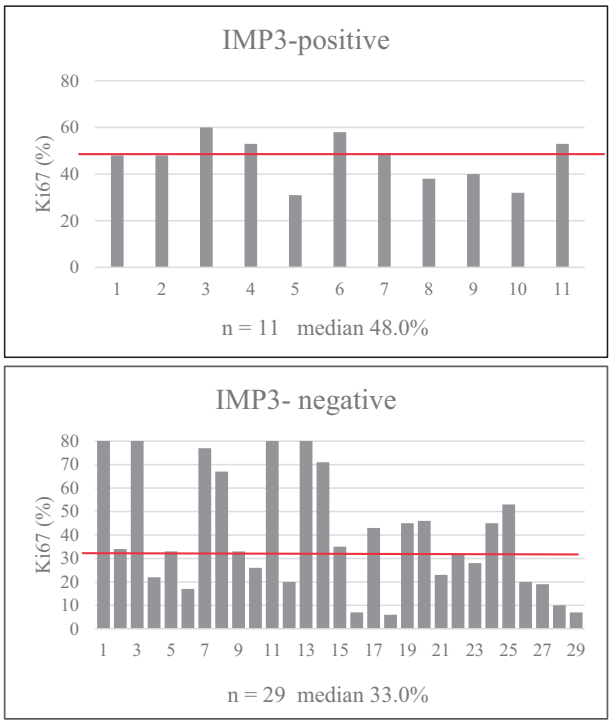


Fig. 2 Distribution of Ki67 (%) in IMP3-positive and IMP3-negative TNBC
Among the 11 IMP3-positive cases, Ki67 (%) ranged from 31% to 60% with a median of 48%. Among the 29 IMP3-negative cases, Ki67 (%) ranged from 6% to 94% with a median of 33%.

negative, 5 (50%) achieved pCR. The difference was not significant (p = 1.0).

Among the 11 patients with IMP3-positive TNBC, the mean Ki-67 labeling index was 46.3% (median, 48.0%). Conversely, in the remaining 29 patients with IMP3-negative TNBC, the mean Ki-67 labeling index was 40.5% (median, 33.0%) (**Fig. 2**).

Although no significant association was found between a Ki-67 labeling index of ≥40% and IMP3 expression (p = 0.119), the Ki-67 labeling index was higher in patients with IMP3-positive TNBC.

Association of IMP3 Status with Glucose Intolerance

Out of the 40 patients, 11 had glucose intolerance, and 5 of these patients were receiving medical treatment for diabetes. There was no correlation between IMP3 expression and glucose intolerance (p = 0.694) and no correlation with diabetes (p = 1.0).

Association of IMP3 Status with DFS

In 11 patients with IMP3-positive TNBC, the mean DFS was 430 (median, 394) days during a median follow-up period of 458 days. Conversely, in 29 patients with IMP3-negative TNBC, the mean DFS was 451 (median, 382) days during a median follow-up period of 667 days. DFS was not significantly different between the patients with IMP3-positive and IMP3-negative TNBC (p = 0.413) (**Fig. 3**).

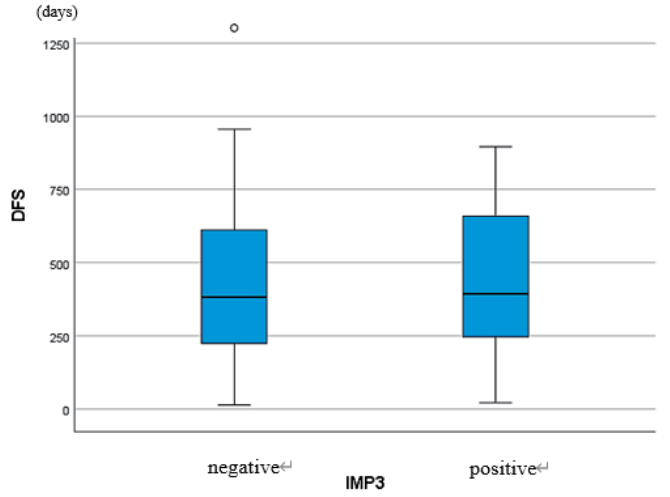
Discussion

IMP3 expression is generally low in normal adult tissues but is elevated in some malignancies. For instance, IMP3 expression was high in 94% of esophageal squamous cell carcinomas[21], 74% of colorectal adenocarcinomas[22], and 50% of metastatic renal cell carcinomas[12]. In breast cancer, IMP3 expression was reported to be positive in 12.8%[23] to 33%[24] of cases. Specifically, this percentage is high in TNBC, with some reports indicating a range of 35.6%[5] to 78%[24]. However, in the present study, the percentage was 27.5%, which is lower than in previous research. Additionally, although some studies have reported a correlation between diabetes and serum IMP3 positivity[25], we found no correlation between impaired glucose tolerance, diabetes, and IMP3 expression in TNBC.

Cellular and nuclear atypia is generally worse for TNBC than for other breast cancer types. Additionally, TNBC is commonly reported to be highly proliferative, with cancer cells being invasive[4]. We hypothesized that these features increase the tendency for more-advanced histologic and nuclear grades.

The prognosis for TNBC is generally poor but may be improved with NAC. Although a recent study reported that IMP3-positive TNBC was resistant to NAC[6], we did not observe NAC resistance in patients with IMP3-positive TNBC in our study cohort. The previous study, from 2017, did not include patients who received dose-dense therapy or immunotherapy. Similarly, none of the patients who received treatments other than dose-dense therapy or immunotherapy achieved pCR. In sum, these findings indicate that achieving pCR may improve outcomes even for patients with IMP3-positive TNBC in the current era in which dose-dense therapy and immunotherapy are increasingly used in clinical practice.

The percentage of cancer stem cells (CSCs) is higher in TNBC than in other breast cancer subtypes[26]. CSCs are a cause of recurrence and drug resistance[27] and can reduce survival[28]. They are present within tumors alongside cancer cells and pose challenges in chemotherapy because of their distinctive abilities. Although chemotherapy eliminates most tumor cells, CSCs may remain, leading to cancer recurrence or treatment resistance[29]. IMP3 is hypothesized to be involved in CSC function[4,30,31]. Development of treatments to target CSCs is a long-standing challenge.



IMP3 status	Number of patients	Mean disease-free survival (days)	Median disease-free survival (days)	Median follow-up (days)
IMP3-positive	11	430	394	458
IMP3-negative	29	451	382	667

Fig. 3 Disease-free survival and follow-up duration in patients with IMP3-positive and IMP3-negative TNBC

Dose-dense therapy enhances treatment efficacy by increasing the frequency of chemotherapy administration. It is based on the Gompertz model of tumor growth and can reduce treatment resistance of tumor cells. Conversely, immunotherapy induces the immune system to attack tumor cells, which may also affect CSCs[32]. Immunotherapy may promote activation of T cells against tumor cells, thereby inhibiting their proliferation and survival[33,34]. Additionally, immunotherapy can enhance immune targeting of tumor cells by preventing the ability of tumor cells to evade the immune system[35].

IMP3 synergistically promotes epithelial-mesenchymal transition and invasiveness, as evidenced by studies reporting its association with increased malignancy potential[36]. However, the present analysis revealed that even patients with high-grade IMP3-positive TNBC had a high likelihood of achieving pCR with recent treatment, suggesting that there is potential for improved prognosis in the current era of enhanced treatment approaches. Our findings indicate that although IMP3 may be an indicator of malignant potential, it is not necessarily a definitive marker of poor prognosis in patients receiving contemporary NAC. In the changing landscape of NAC regimens for TNBC, our understanding of the complex nature of CSCs and the mechanisms of treatment resistance remains incomplete. Further studies of the effects of dose-dense therapy and immunotherapy on CSCs are therefore warranted.

The present study cohort included a limited number of patients who received dose-dense therapy or immunotherapy, which is a significant limitation; thus, future studies with larger cohort sizes are necessary. Additionally, not all patients received dose-dense therapy or immunotherapy. The development of novel therapeutic approaches targeting IMP3 or CSCs might potentially improve outcomes for patients with TNBC.

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Conflict of Interest: The authors declare no conflicts of interest.

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