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The Utility of MT1-MMP in Predicting Treatment Efficacy with HER2-positive advanced or metastatic breast cancer: JBCRG-M06/EMERALD trial TR

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Background

Malignant tumor cells grow invasively and form distant metastases after moving through multiple tissue barriers. Invasion requires cell locomotion, accompanied by the degradation of the extracellular matrix (ECM) by matrix metalloproteinases (MMPs). It is reported that MT1-MMP (Membrane Type 1 MMP) cleaves type Ⅰ collagen and activates type Ⅳ collagenase MMP-2, which promotes tumor malignancies via ECM remodeling. However, most of the MT1-MMP studies were in basic science; it remains unclear whether MT1-MMP protein levels correlate with drug treatment in patients. Here, we conducted a retrospective analysis of MT1-MMP on treatment effectiveness and survival using JBCRG-M06/EMERALD clinical trial.*

*T. Yamashita et al, J Clin Oncol, 2024;43(11):1302-1313

Method

- EMERALD study is a Phase III study comparing two first-line chemotherapeutic treatments for HER2-positive local advanced or metastatic breast cancer: trastuzumab, pertuzumab, and taxane therapy versus trastuzumab, pertuzumab, and eribulin mesylate therapy.
- In EMERALD study, 231 specimens were collected from 231 patients who consented to biomarker research at the time of enrollment.
- The tissue samples were immunostained with anti-MT1-MMP antibody and classified into score1/2/3 expression based on staining proportion and intensity.
- Investigated the relationships between MT1-MMP expression and therapeutic effects of drugs (e.g. ORR, PFS).

Result

Characteristics

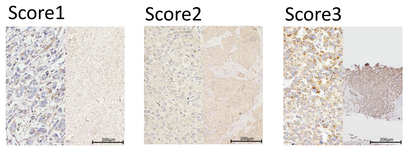
	Eribulin group n=123	Taxane group n=108
Age, years(range)	56.0(29-70)	56.0(34-70)
ER status(%)		
positive/negative	71(57.7)/52(42.3)	54(50)/54(50)
Stage(%)		
metastatic recurrent/de novo StageⅣ	54(43.9)/69(56.1)	42(38.9)/66(61.1)
Visceral metastasis(%)		
yes/no	77(62.6)/46(37.4)	78(72.2)/30(27.8)
Specimen(%)		
primary tumor/metastatic site	97(78.8)/26(21.2)	85(78.7)/23(21.3)
MT1-MMP score(%)		
1/2/3	28(22.8)/52(42.3)/43(34.9)	26(24.1)/43(39.8)/39(36.1)
metastatic recurrent 1/2/3	21(38.9)/24(44.4)/9(16.7)	20(47.6)/19(45.2)/3(7.1)
de novo StageⅣ 1/2/3	7(10.1)/28(40.6)/34(49.3)	5(7.6)/24(36.4)/37(56.0)

Multivariate analysis

	hazard ratio	95%CI	p-value
ER status	1.0030	0.7283-1.3820	0.9835
Stage	1.1490	0.6510-2.0260	0.6326
Visceral metastasis	1.1360	0.8108-1.5910	0.4591
treatment	1.0300	0.7541-1.4070	0.8531
MT1-MMP score	0.7728	0.6071-0.9838	0.03635

Cox hazard model

MT1-MMP score

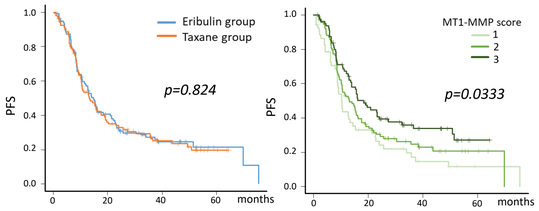


Proportion >50%
Intensity
Score1: low
Score2: intermediate
Score3: high

Best overall response

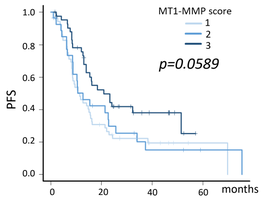
	Eribulin group n=123			Taxane group n=108		
MT1-MMP score	1	2	3	1	2	3
CR	5	6	5	4	4	6
PR	13	34	33	9	30	27
SD	6	9	4	8	8	6
PD	2	3	1	4	1	0
NE	2	0	0	0	0	1
ORR	64.3%	76.9%	88.4%	52.0%	79.1%	82.5%
	Total 78.0%			Total 74.1%		

PFS of All patients

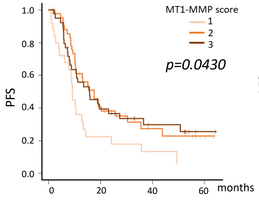


There was no difference between eribulin and taxane groups in PFS.
However, higher MT1-MMP scores tended to improve PFS.

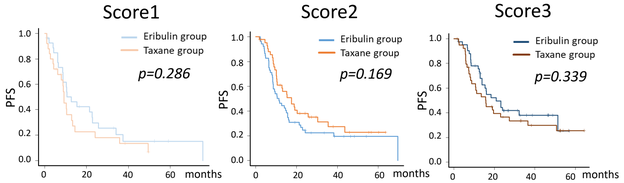
PFS in Eribulin group



PFS in Taxane group



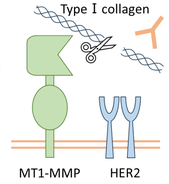
PFS by MT1-MMP score



There was no difference between eribulin and taxane groups in PFS by MT1-MMP score.

Discussion

MT1-MMP is more abundant in cancer cells, where it cleaves type Ⅰ collagen and activates MMP-2; therefore, it is considered a marker of increased malignancy. Based on TCGA data, MT1-MMP mRNA expression levels were correlated with poor survival rates in Lung carcinoma, but not in Breast cancer. Although TCGA data are powerful, they contain multiple biases, such as cohort bias and sample bias. In this study, we confirmed that MT1-MMP protein levels are affected by drug treatment using clinical samples by IHC. Higher MT1-MMP scores tended to be associated with higher ORR and longer PFS. We are considering two possibilities: 1. MT1-MMP correlates with malignancies, as previously reported, and malignant cancers tend to respond well to drugs.
2. Recently, it has been reported that microenvironmental remodeling by cancer cells affects drug response. Therefore, we hypothesize that MT1-MMP cleaves collagen and modulates the microenvironment, facilitating the physical transport of larger drugs, such as antibodies, to cancer cells.



Conclusion

- MT1-MMP score is unable to distinguish the combined trastuzumab and pertuzumab with eribulin mesylate or trastuzumab and pertuzumab with taxane therapy.
- However, MT1-MMP score may be a prognostic factor for HER2-positive local advanced or metastatic breast cancer patients.

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