



High BIM mRNA levels associated with longer survival in advanced gastric cancer

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ABSTRACT

Background: 5-fluorouracil, oxaliplatin, and docetaxel chemotherapy are commonly used in the treatment for gastric cancer (GC). Apoptosis relevant genes might be associated with drug resistance. Approximately half of the patients could be the candidates for second-line treatment at the time of failure to first-line chemotherapy. Docetaxel is among the most frequently used agents for gastric second-line treatment.

Methods: We investigated mRNA expression levels of BIM, AEG-1 and AXL in 131 advanced gastric cancer samples and correlated gene levels with patients' overall survival. All 131 patients received first-line FOLFOX chemotherapy, in which 56 patients were further treated with second-line docetaxel-based chemotherapy.

Results: Correlation between BIM mRNA expression and AEG-1 mRNA expression was observed ($r_s = 0.30$, $P = 0.002$). There is no association between mRNA expression levels of any of the individual genes and overall survival in patients only receiving first-line FOLFOX chemotherapy. In a subgroup of patients receiving docetaxel-based second-line chemotherapy, those with high or intermediate levels of BIM obtained a median overall survival of 18.2 months (95% CI=12.8-23.6), compared with 9.6 months (95% CI=8.9-10.3) in patients with low BIM levels ($P = 0.008$). However, there was no correlation between AEG-1, AXL mRNA expression and overall survival. The risk of mortality was higher in patients with low BIM mRNA levels compared with high or intermediate levels ($HR = 2.61$, 95% CI=1.21-5.62, $P = 0.01$).

Conclusions: BIM could be considered as a biomarker to identify whether patients can benefit from docetaxel-based second-line chemotherapy in gastric cancer

BACKGROUND

- The incidence of gastric cancer ranks as the fifth most frequent cancer worldwide. Nearly 40% of gastric cancer occurs in China.
- The median overall survival (OS) remains less than 12 months with first-line oxaliplatin, 5-fluorouracil (FU), and folinic acid (FOLFOX) treatment.

- Docetaxel is among the most frequently used agents for gastric second-line treatment.
- BIM plays as a pivotal regulator of the mitochondrial apoptosis pathway. Our previous work found patients with high BIM expression achieved longer survival in EGFR-mutant NSCLC treated with erlotinib or chemotherapy.
- AEG-1 overexpression correlated with poor prognosis in gastric cancer and NSCLC.
- Overexpression of AXL was responsible for tumor growth and increased AXL activation had been reported to be linked with cisplatin resistance in ovarian cancer

PATIENTS AND METHODS

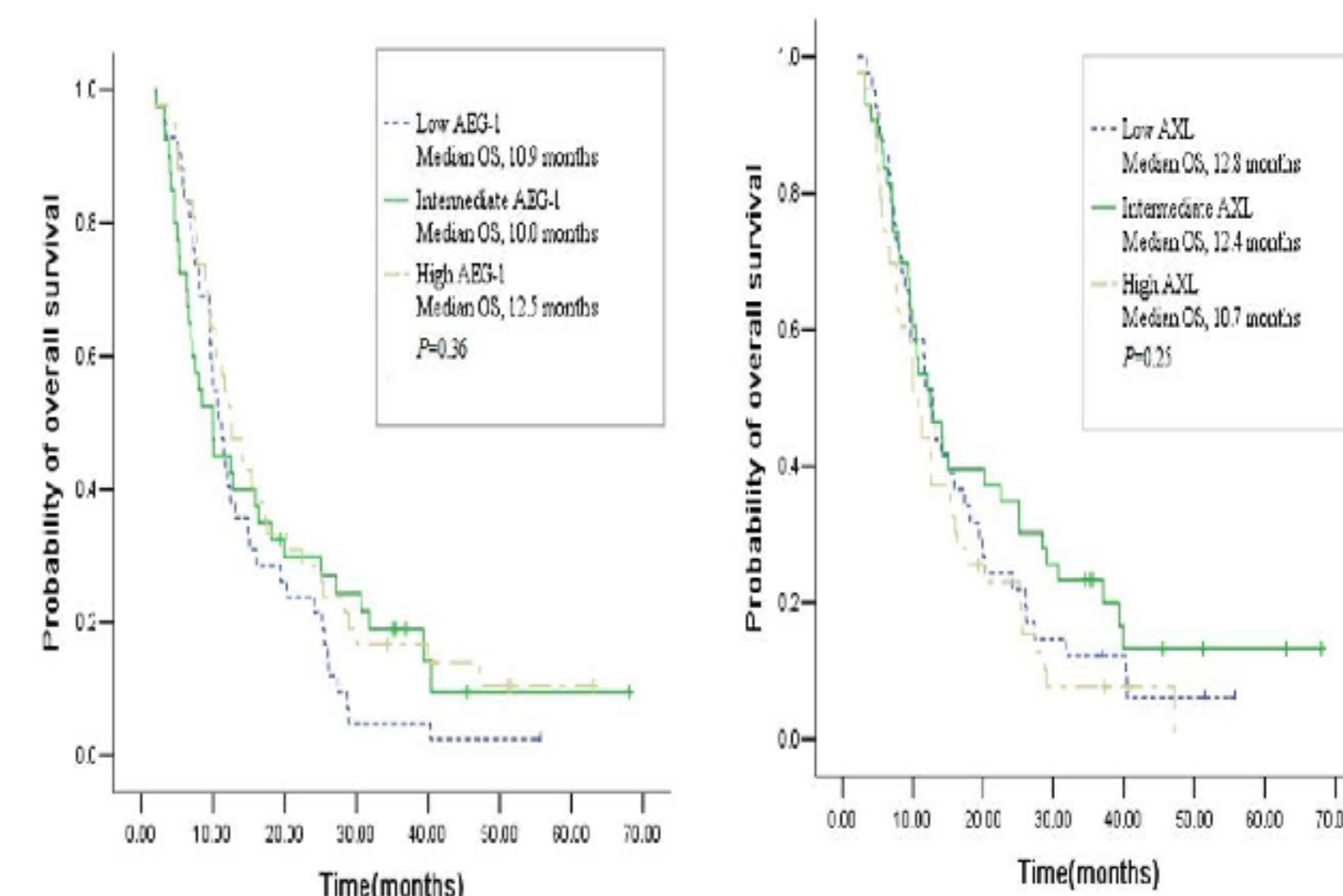
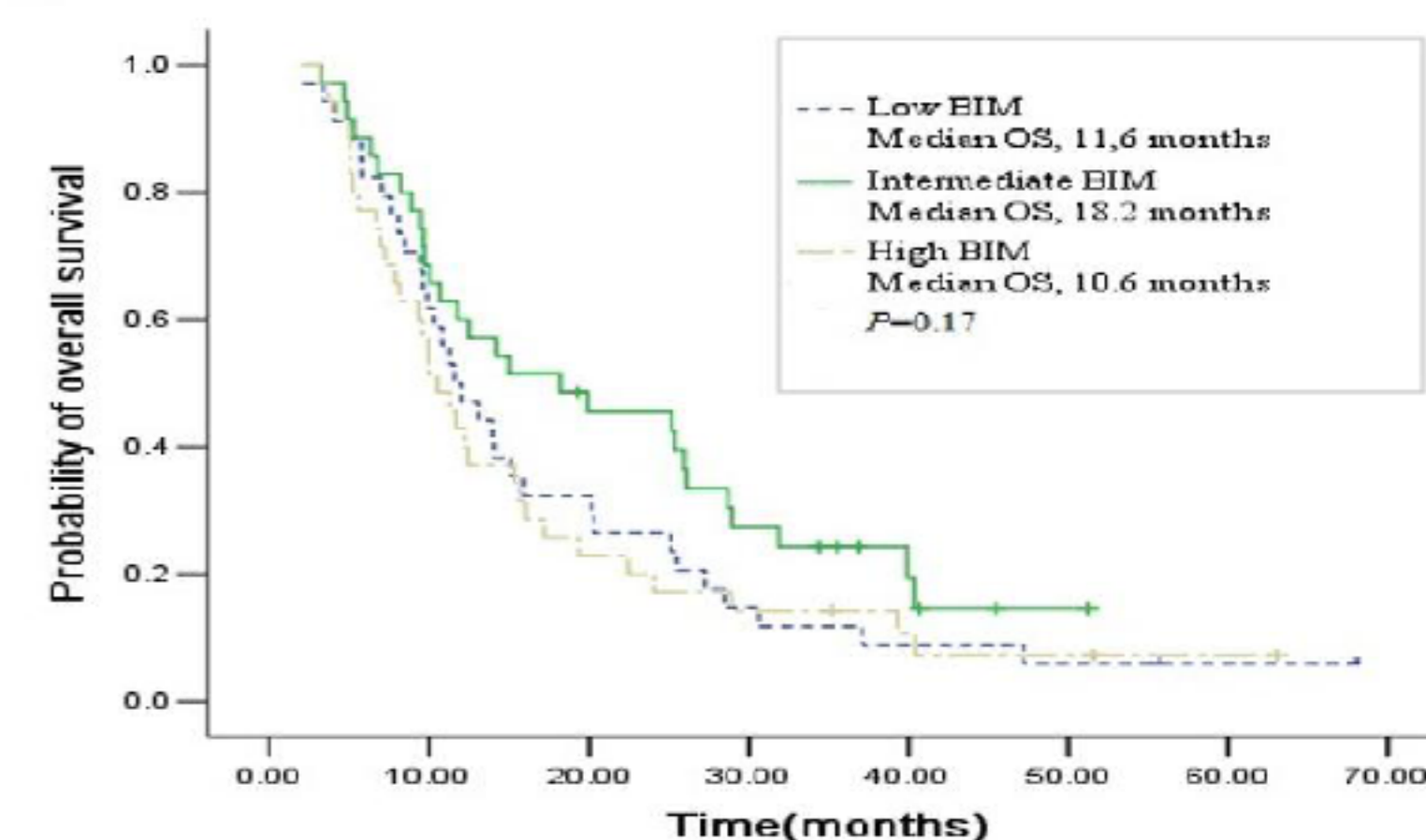
- A total of 131 advanced gastric cancer samples were included in this study.
- Gene expression profiling was performed on RNA isolated from the macrodissected tumor tissue contained at least 80% tumor cells.
- Gene expressions were analyzed as categorical variables by tertiles

RESULTS

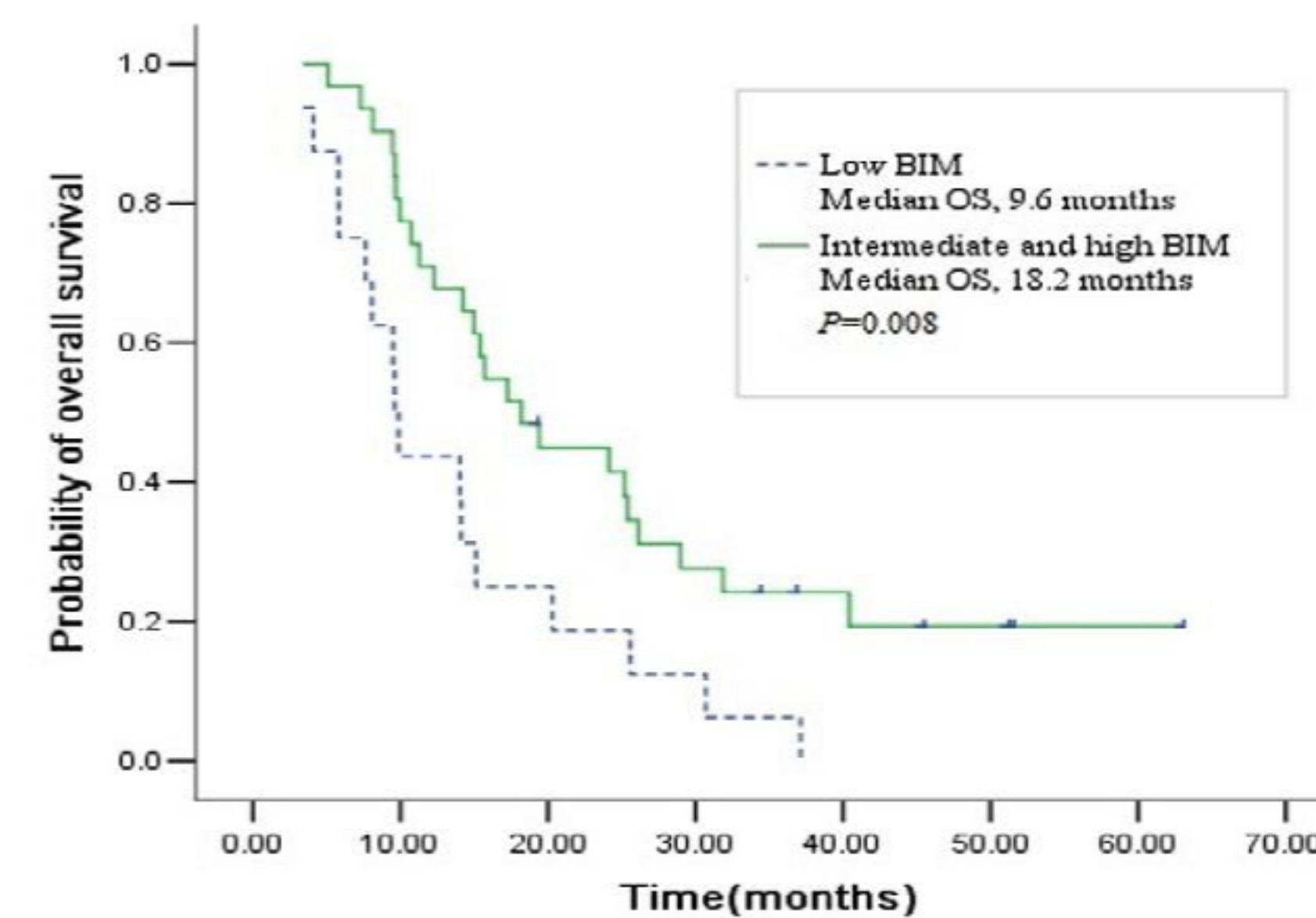
Patient characteristics

Characteristics	All patients (N=131)	Patients receiving first-line therapy (N=75)	Patients receiving second-line therapy (N=56)	P
Age				0.33
<60	63 (48.1%)	32 (42.7%)	31 (55.4%)	
≥60	68 (51.9%)	43 (57.3%)	25 (44.6%)	
Sex				0.41
Female	31 (23.7%)	20 (26.7%)	11 (19.6%)	
Male	100 (76.3%)	55 (73.3%)	45 (80.4%)	
Tumor site				0.27
Distal stomach	50 (38.5%)	25 (33.8%)	25 (44.6%)	
Proximal stomach	38 (29.2%)	24 (32.4%)	14 (25.0%)	
Whole stomach	42 (32.3%)	25 (33.8%)	17 (30.4%)	
Stage				0.55
III	79 (60.3%)	44 (58.7%)	35 (62.5%)	
IV	52 (39.7%)	31 (41.3%)	21 (37.5%)	
ECOG PS				0.39
0-1	119 (90.8%)	66 (88.0%)	53 (94.6%)	
2	12 (9.2%)	9 (12.0%)	3 (5.4%)	
Histological grade				0.07
G2	35 (27.1%)	20 (27.0%)	15 (27.3%)	
G2-3	35 (27.1%)	17 (23.0%)	18 (32.7%)	
G3	59 (45.7%)	37 (50.0%)	22 (40.0%)	

Kaplan–Meier estimates of overall survival in all patients according to BIM/ AEG-1/AXL mRNA levels



Kaplan–Meier estimates of overall survival in patients receiving docetaxel-based second-line chemotherapy according to BIM mRNA levels



CONCLUSIONS

- Due to significantly prolonged overall survival among patients with high or intermediate BIM mRNA expression in our study, BIM can act as a potential biomarker in second-line docetaxel based chemotherapy for gastric cancer.

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