New prognostic factors in gastric cancer: the role of lympho-plasmacytic infiltrate

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New prognostic factors in gastric cancer: the role of lympho-plasmacytic infiltrate.

BACKGROUND: *Gastric cancer triggers an immune response, manifested by immunocompetent cells infiltrating the tumor, such as macrophages, NK cells, neutrophils, T and B-lymphocytes, and plasma cells.*
METHODS: *Were viewed 300 patients who received surgery for gastric cancer, with removal of at least 15 regional lymph nodes, from January 1998 through December 2008, at the Policlinico "Umberto I", Department of Surgery "Pietro Valdoni", "Sapienza" University of Rome, and at "Santa Maria Goretti" Hospital of Latina, Italy. We selected a subset of 46 patients identified according to the following selection criteria: presence of gastric cancer (both intestinal-type and diffuse-type), early-stage (T1 and T2), absence of nodal metastases (N0), or involvement of less than 8 lymph nodes (N1), absence of distant metastases (M0), stage I and II. The sample included 28 males and 18 females.*
RESULTS AND CONCLUSIONS: *Our results suggest that a high number of tumour-associated macrophages (TAM) along the margins of the tumour is related to a worse outcome, and an increased secretion of immunosuppressive cytokines by TAM may also indirectly affect the action of cytotoxic T cells. Our study also shows a statistically non significant trend of tumour-associated macrophages in promoting the expression of β-catenin, which is a subunit of the cadherin protein complex.*

KEY WORDS: Gastric cancer, Infiltrate, Lymphoplasmacellular, Prognostic factors, TNM

Introduction

Gastric cancer, remains a major public health issue as the fourth most common cancer and the second leading cause of cancer death worldwide. Many works study its characteristics and treatment patterns [1]. Gastric cancer, just like anyother tumour, triggers an immune response, including the infiltration of the tumour by immune cells, such as macrophages, NK cells, neutrophils, T helper cells, cytotoxic T cells its margins, each one of the different cellular subsets playing a different role in limitin, B-lymphocytes, and plasma cells. This infiltrate can deeply involve the neoplasm and/or g growth and spread of the neoplasm [2-3]. The use of monoclonal antibodies allows both quantitative and morphological characterisation of these sub-populations and detection of their localisation within the tumour. Therefore, by matching these results with the clinical and histopathologic features of every single patient, we can identify new prognostic factors of gastric. To date, the modalities of communication between the different plasma cells, and their importance in anti-tumour monitoring and the invasion and spread of cancer have been clarified [4-5]. These anti-tumour featuresrely very much on tumour immunogenicity, which, in turn, depends on theamount of mutations of neoplastic cells. Cancers such as colorectal cancer bear many mutations, mainly related to the instability of microsatellites, while gastric tumours have only

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a few, which helps these to escape the host immune response [6]. In relation to the different lymphocytic subpopulations, in antitumor surveillance, macrophages such as tumour-associated macrophages (TAM, recognized by the presence of the antigen CD68 on their surface) are, directly or indirectly, responsible for the suppression of T lymphocytes activated against tumour cells [7]. The tumour-associated macrophages are an essential component of tumour infiltrating leukocytes, representing a double-edged sword, with the potential to express both pro- tumour and anti-tumour activity, with the for more prevailing in well established neoplasms [8-9]. A study on transgenic mice has suggested that activated macrophages play an important role in gastric tumourigenesis through the promotion of Wnt / β-catenin [8]. In fact, gastric canceris strongly associated with Helicobacter pylori (HP) infection, which involves chronic inflammation of the stomach [10],while the activation of the Wnt/β-catenin signal is reported in about 30% of gastric cancers [11]. HP infection in transgenic mice causes an infiltration of macrophages and activation of the Wnt / β-catenin in the gastric mucosa, thus leading to tumourigenesis [12]. Natural killer (NK) cells (CD57+) belong to the immune system and non-specifically act against cancer. A high number of infiltrating NK cells was frequently observed in patients with "early gastric cancer", with poor or no nodal involvement. In these cases, there are fewer NK cells inside the tumour, and most of these are found around the neoplasm. In contrast, in large, infiltrating tumours, there are few NK cells both within and around the lesion. NK cell infiltration is, therefore, inversely related to the depth of tumour invasion, the clinical stage, and lympho vascular spread. Survival rates in patients with stronger NK cell infiltration also seem to be better [13]. The cytotoxic T lymphocytes (CD8+) play a crucial role in limiting growth and spread of the tumour. The level of cellular tumour infiltration is quantitatively different in the two histological types of gastric cancer, intestinal and diffuse. In the intestinal subtype, cells are broadly described within the infiltrate, while, in the diffuse subtype, immunosuppression is generally more pronounced, and the number of CD8+ cells present is low. In addition, it has been shown that those lymphocytes located in the tumour epithelium can have a positive prognostic effect while those located in the stroma or along the margins of the neoplasm have no effect on prognosis [14]. One of the most important and currently studied variables is localisation of immune-cells in relation to tumour tissue, which, accordingly, is classified as intratumoural-intraepithelial, peritumoural, and stromal. In fact, it is believed that, depending on their location; the different cellular subpopulations can be exposed to the effect of multiple substances, especially inflammatory mediators, which alter their function and response, thusentailing different prognostic outcomes [15].

Materials and Methods

Were viewed 300 patients who received surgery for gastric cancer, with removal of at least 15 regional lymph nodes, from January 1998 through December 2008, at the Policlinico "Umberto I", Department of Surgery "Pietro Valdoni", "Sapienza" University of Rome, and at "Santa Maria Goretti" Hospital of Latina, Italy. From this group, we selected a sub-set of 46 patients identified according to the following selection criteria: presence of gastric cancer (both intestinal-type and diffuse-type), early-stage (T1 and T2), absence of nodal metastases (N0), or involvement of less than 8 lymph nodes (N1), absence of distant metastases (M0), stage I and II. The sample included 28 males and 18 females, with the following age characteristics: Overall Range=41-92 years, Mean=64.9 years. Males: Range=41-83 years, Mean=64.8 years. Females: Range=40-92 years, Mean=65 years (Table I). Follow-up was of mean=57.53 months (range=24-88 months). Of the studied 46 patients, 17 died (37%, 11 males and 6 females), 11 (24%) for recurrence of the tumour and / or for metastases, 6 (13%) for tumour un related causes. Survival was: range=1-84

TABLE I - *Clinical and histopathological features of studied population (n=46)*

Features	**Patients n (%)**
Gender	
Males	28 (60)
Females	18 (40)
Tumour	
T1	11 (24)
T2	33 (72)
T3	2 (4)
Lymphnodes	
N-	21 (45,.6)
N+	25 (55.4)
Differentiation	
G1	4 (8)
G2	18 (30)
G3	24 (52)
Lymphoplasmacellular Infiltrate	
Poor	14 (30)
Moderate	22 (48)
Severe	10 (21)
Lauren's Classification	
Intestinal	29 (63)
Diffuse	14 (30)
Mixed	3 (7)
Signet Ring Cells	
Yes	16 (34)
No	30 (66)

months, mean=30.91 months. Only 6 patients of the entire group received post-operative adjuvant chemotherapy: of these, one died 24 months after surgery, while the other five were followed, respectively, for 36, 40, 84, 85, and 88 months after surgery (Table I). The preparations of the primary tumour, previously embedded in paraffin, were sectioned with a thickness of 4 m and then examined with immunohistochemistry by means of specific monoclonal antibodies, in order to identify and study the various sub-populations present in peri-and intratumour lymphoplasmacellular infiltrate. These subpopulations are mainly represented by immunocompetent cells that are divided, in relation to the expression of adhesion molecules on the membrane, in CD8+ (cytotoxic T lymphocytes), CD68+ (macrophage), and CD57+ (Natural Killer cells). The slides were stained with diaminobenzidine. The marked cells were there after quantified with 400x magnification in 15 different fields. Expression of β-catenin in tumour cells, at the level of cellular membrane, cytoplasm and nucleus, was evaluated and correlated with the infiltration of tumour-associated macrophages. Finally, the patients were divided into two subgroups according to the number of cells of each subpopulation,respectively lower or higher than the median (Group A< n, group B ≥ n). Lymphoplasmacellular infiltrate was classified, on the basis of localization, in peritumoural (along theedges of infiltration) and intratumoural / intraepithelial.

Immunohistochemistry

For immune histochemic alanalysis, the following antibodies were employed:
– Anti-CD8 (monoclonal, clone 1A5, 1:20 dilution, Novocastra™, Leica Biosystems, Milan, Italy);

Table II - *Distribution of CD8+ cells and associated clinical and pathological features of relevant population (mean ± standard deviation, t Student's test) (p < 0.05)*

Features (n)	**CD8+ Intra**		**Peri**	
		*p**		*p**
Age (years)				
< 65	20.23 ± 30.56 (10)	0.224	196,94 ± 117,32 (175,5)	0.942
≥ 65	10.50 ± 11.38 (6)		194,13 ± 113,83 (205,5)	
Gender				
Males	17.23 ± 25.76 (10)	0.432	196.19 ± 105.71 (189.00)	0.538
Females	11.29 ± 13.34 (5.50)		175.00 ± 121.53 (163.50)	
Tumour				
pT1	18.71 ± 11.16 (14)	0.647	229.70 ± 138.32 (224)	0.183
pT2	14.36 ± 24.02 (5.50)		174.52 ± 104.69 (152)	
pT3			195.50	
Differentiation				
G1	120.33±92.59(104)	0.283	14	0.653
G2	170.83 ± 101.03 (172)		16.81 ± 17.98 (9.50)	
G3	208.79 ± 119.12 (194)		13.37 ± 17.39 (7)	
Lymphnodes				
Negatives	19.80 ± 28.53 (12)	0.485	209.66 ± 100.66 (219)	0.216
Positives	11.43 ± 15.08 (7)		168.33 ± 118.68 (146)	
Lauren's Classification				
Intestinal	19.57 ± 25.97 (13)	0.478	188.14 ± 118.41 (200.5)	0.932
Diffuse	7.64 ± 5.30 (9)		185 ± 99.15 (170)	
Mixed	7.64 ± 5.30 (1.5)		196 ± 141.26 (244)	
Lymphoplasmacellular infiltrate				
Poor	22 ± 34.17 (8)	0.293	158.53 ± 96.08 (125)	0.442
Moderate	12.13 ± 12.20 (10.50)		184.80 ± 100.98 (204)	
Severe	9.88 ± 8.89 (9.50)		237.20 ± 143.82 (242)	
Signet ring cells				
Yes	12 ± 12.06 (9.50)	0.637	190.44 ± 120.33 (164.50)	0.904
No	16 ± 24.61 (8.50)		186.17 ± 108.42 (202)	

TABLE III - *Distribution of CD57+ and of CD68+ peritumoural and intraepithelial cells, and associated clinical and pathological features of relevant population(mean ± standard deviation, t Student's test) (p< 0.05)*

Features (n)	CD57+ Intra	CD68+ Peri	p*	Intra	p*	Peri	p*		p*
Age (years)									
< 65	7.08 ± 8.22 (5)	0.206		70.71 ± 38.66 (72)	0.224	21.20 ± 14.38 (16)	0.436	176.23 ± 126.48 (158)	0.311
≥ 65	4.33 ± 4.22 (3)			54.74± 41.58 (36)		17.27 ± 12.04 (14.50)		220.09 ± 113.85 (212.50)	
Gender									
Malesi	4.08 ± 3.98 (3)	0.161		52.42 ± 36.40 (39)	0.146	20 ± 11.52 (18)	0.398	198.35 ± 129.44 (170)	0.665
Females	6.86 ± 8.01 (4.50)			70.07 ± 43.03 (72)		16 ± 14.68 (13.50)		213.64 ± 104.81 (217)	
Tumour									
pT1	6.6 ± 9.66 (3)	0.374		59.91 ± 49.03 (31)	0.947	15.63 ± 13.04 (10.50)	0.492	141.63 ± 95.73 (101)	0.076
pT2	4.63 ± 3.84 (4)			58.97 ± 37.34 (47)		19.41 ± 13.20 (15.50)		229.88 ± 124.17 (239)	
pT3						20		241.50	
Differentiation									
G1	3	0.352		50.50	0.174	11	0.266	91.25	0.485
G2	6.40 ± 8.30 (3)			69.53 ± 42.31 (73)		16.42 ± 13.36 (14)		205.09 ± 85.75 (268)	
G3	4.45 ± 3.59 (4)			53 ± 34.04 (44)		21.94 ± 12.21 (19)		237.10 ± 135.39 (315)	
Lymphnodes									
Negatives	5.65 ± 7.52 (3)	0.614		62.71 ± 40.13 (51)	0.564	17.36 ± 13.48 (13)	0.662	211.35 ± 139.87 (190)	0.964
Positives	4.67 ± 4.19 (4)			55.79 ± 39.55 (39)		19.39 ± 12.41 (17)		209.44 ± 105.45 (217)	
Lauren's Classification									
Intestinal	6.52 ± 7.00 (5)	0.065		66.32 ± 42.51 (55)	0.177	14.44 ± 10.30 (14)	**0.003**	201.05 ± 113.36 (235)	0.470
Diffuse	2.58 ± 1.62 (2.5)			48.93 ± 29.22 (41.5)		28,27 ± 12.08 (28)		233.46 ± 135.92 (199)	
Mixed	4.33 ± 4.16 (3)			38 ± 47.82 (21)		7 ± 2 (7)		169.33 ± 129.96 (104)	
Lymphoplasmacellular infiltrate									
Poor	5.86 ± 7.55 (4)	0.638		66.32 ± 42.51 (55)	0.177	23.27 ± 14.75 (26)	0.371	220.82 ± 132.15 (171)	0.349
Moderate	4.76 ± 5.29 (3)			48.93 ± 29.22 (41.5)		18.53 ± 11.80 (16)		174.81 ± 116.46 (180)	
Severe	4.43 ± 3.26 (5)			38 ± 47.82 (21)		9.67 ± 5.82 (8.50)		267.13 ± 104.72 (186.50)	
Signet ring cells									
Yes	6.75 ± 8.75 (3.50)	0.245		67.50 ± 39.40 (61.50)	0.290	19.90 ± 14.18 (13.50)	0.681	213.09 ± 144.26 (145)	0.930
No	4.35± 3.88 (4)			54.34± 39.48 (37)		17.86 ± 12.30 (15.50)		209.13 ± 113.02 (237)	
β- cateninexpression									
Preserved	6.10 ± 5.22 (4.50)	0.590		68.25 ± 47.29 (58.50)	0.303	11.75 ± 7.72 (11.50)	**0.021**	223,55 ± 100.78 (190)	0.811
Alterated	4.88 ± 6.30 (3.50)			54.31 ± 36.27 (41.50)		22.05 ± 13.39 (18.00)		213 ± 127.25 (239)	

– Anti-CD57(monoclonal, clone NK-1, 1:50 dilution, Novocastra™, Leica Biosystems, Milan, Italy);
– Anti- CD68 (monoclonal, clone KP1, dilution 1:400, Novocastra™, Leica Biosystems, Milan, Italy);
– Anti- β-catenin (monoclonal, clone 14, dilution 1:500, Transduction Laboratories, Lexington, KY, USA).

Immunohistochemistry was performed on tissue sections fixed in formalin and embedded in paraffin. These sections were collected on glass slides with positive polarity, placed in the oven for 5 minutes at 50°C, dewaxed in xylene and then rehydrated, using alcohol with progressively lower concentration, up to water. Blocking of endogenous peroxidase was achieved with a 5-minute-bath of 3% hydrogen peroxide for all samples, except for the anti-CD4 antibody. In the latter instance, the same operation was performed by using a 5 minute bath of hydrogen peroxide / methanol 0.5 %. The antigenic sites were evidenced for all antibodies by heat treatment, using the microwave oven at 750 W,for 3 cycles of 5 minutes each, in a solution of citrate buffer at pH 6, followed by a cooling period of 20 minutes at room temperature. The sections were covered with diluted normalserumready to use (RTU) (Normal Horse Serum, Vector Laboratories, Burlingame, CA, USA) for 10 minutes and then incubated with 100 ml of primary antibody for 60 minutes at room temperature, after rinsing with distilled water. Rinsing with phosphate buffered saline (PBS), was performed twice for 5 minutes each time, and then the sections were incu-

TABLE IV - *Relationship between distribution of CD8+, CD57+, and CD68+ cells and survival (log-rank test).*

	CD8+ Peri		CD57+ Intra		Peri		Intra		CD68+ Peri		Intra			
	A		B		A		B		A		B		A	B
Mean survivals:														
Months (no. patients)	27.13(46)		34.69(46)		25.81(46)		35.58(46)		26(46)		36.60(46)		22.88(46)	36.07(46)	45.64(46)	23(46)	40.45(46)	32.5(46)
p	0.131		0.132		0.074		0.048		0.179		0.291							

bated for 30 minutes with two or three drops of biotinylated secondary antibody (RTU Biotinylated Universal Antibody, Vector Laboratories, Burlingame, CA, USA), and after further rinsing with PBS, each slide was incubated for 30 minutes at room temperature with two or three drops of serum containing the complex Avidin / Biotin (RTU Vectastain™, Elite ABC Reagent, Vector Laboratories, Burlingame, CA, USA).The sections, againrinsed twice with PBS for 5 minutes each, were incubated for 5-10 minutes with a solution of the chromogenic substrate, diaminobenzidine (DAB), and finally counterstained in Meyer 's haematoxylin (Merck, Darmstadt, Germany) for 7 seconds, dehydrated in increasing alcohol series, clarified in xylene, and mounted in syntheticresin.

Statistical Analysis

The intratumoural and peritumoural lymphocyte subpopulations were further sub-divided into two subgroups, based on low or high density of lymphoplasmacellular infiltrate, selecting, as there ferencevalue, the median *m* of eachgroup(group A<*m*, group B ≥ *m*). In addition, by means of computerized statistical tests, multivariate analysis was performe dusing Student's t-test and χ^2-test. Finally, the prognostic impact of the various cellular subsets wase valuated by using the Kaplan-Meier and log ranktests. Statistical significance was considered in cases with $p<0.05$.

Results

The lymphoplasmacellular infiltrate was morphologically characterized, using monoclonal antibodies, in CD8+ cells (Tc lymphocytes), CD57+ (Natural Killer cells), and CD68+ (macrophages), and there after further subdivision based on location and in peri- or intratumoural / intraepithelial features was performed. Expression of β-catenin, especially in relation to infiltration of tumour-associated macrophages, was also evaluated. After quantitative assessment of the number of cells labelled with 400x magnification in 15 different fields for each of the two groups, the sample was divided into two subgroups, respectively below and above the median (m) (subgroup A< m, subgroup B ≥ m). The study was focused, therefore, on the CD8+, CD57+ and CD68+, and on the expression of catenin. The distribution of intra- and peritumoural CD8+, CD57+, and CD68 +, eachdistinct in subgroups A and B, was associated with the following clinical and histological parameters: patient's age, extent of the primary tumour, presence of lymph node metastases, degree of differentiation of tumour cells, tumour histological type according to the Lauren's classification, the presence of signet ring cells. Distributions were also collated with survivals, by means of the survival curve of patients with the Kaplan-Meier method. Finally, distributions were compared with the survival curves of groups A and B for the individual lymphocytic subpopulations, intra-and peritumoural, using the log-ranktest.

Results of the Subgroups

CD8+ cells (cytotoxic T lymphocytes)

Most of the CD8+ cells were distributed along the margins of tumour invasion,while inside the tumour very small quantities were detected (mean=185.96 and 17.24 cells, respectively, for 15 fields). Statistical analysis revealed no significance in relation to the considered factors, both for peritumoural and for intratumoural cells (Table II).

CD57+ cells (Natural Killer)

Natural Killer cells were more represented along the margins of infiltration (mean= 58.27 cellsfor 15 fields) compared to the inside of the tumour (mean=5.67 cellsfor 15 fields). Statistical analysis did not show significant differences between the parameters taken into consideration.

CD68+ cells (macrophages)

The pattern of distribution of CD68+ cells was similar to that of CD8+ and of CD57+ cells (mean=224.39 cells along the margins of tumour infiltration, vs. mean=16.04 cells inside the tumour).

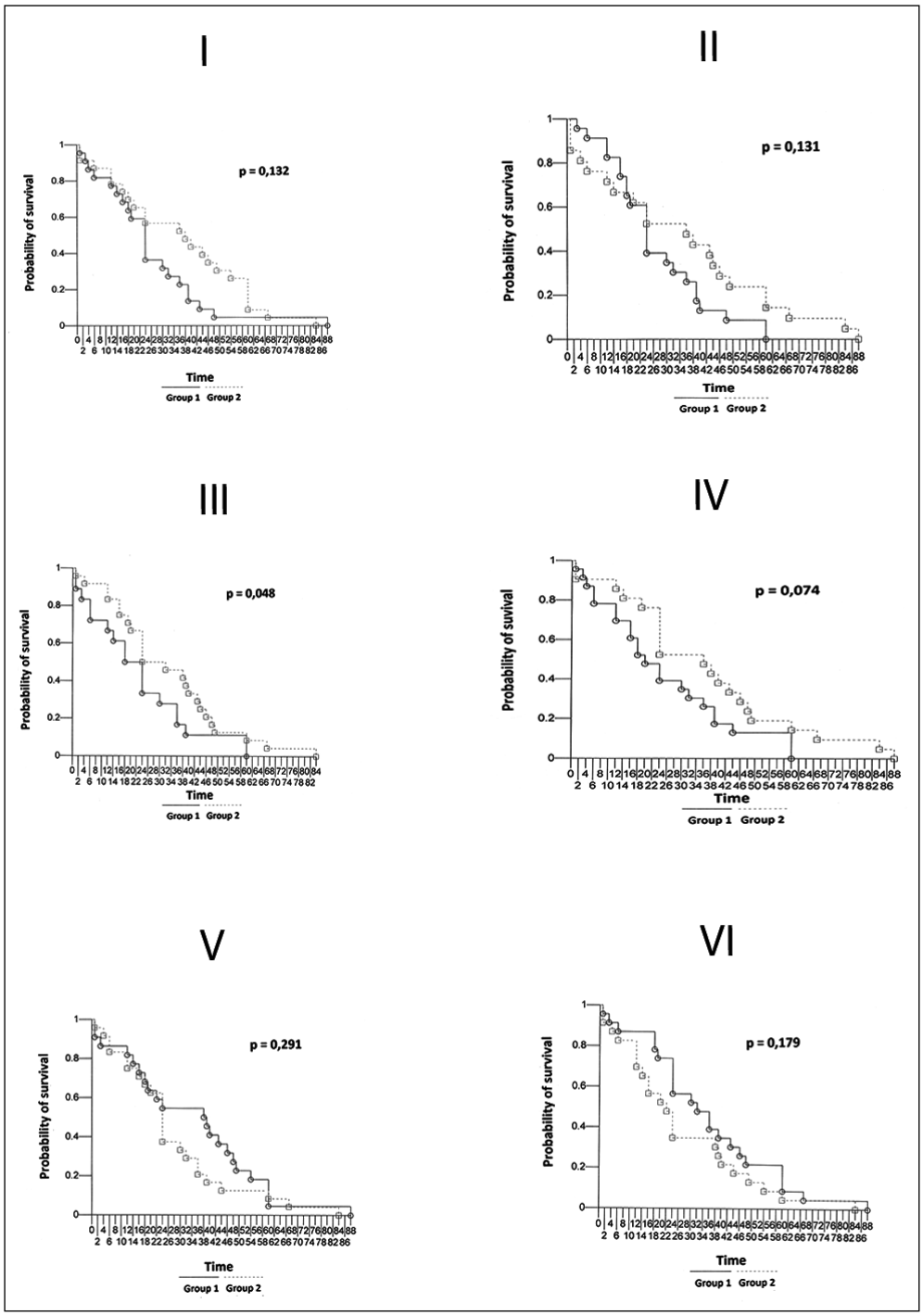

Fig.: 1

Diffuse gastric cancer proved to have a statistically different concentration of intratumoural macrophages, compared to the intestinal sub-type (p=0.003, Student's t test), and also the expression of -catenin was significantly increased in relation to the number of intratumoural macrophages (p=0.021, Student's t test) (Table III). The analysis of the survival curves of the individual subgroups revealed a better outcome in patients with lower peritumoural infiltration of CD68+ cells, although his valuedid not reach significant levels (p= 0.179) (Table IV). A better outcome was also found in patients with fewer macrophages and preserved -catenin expression, albeit, also in this case, without statistical significance (p=0.394) (Figs. 1, 2).

Discussion

In our series, the infiltrating immunocompetent cells were spread both along the margins of tumour infiltra-

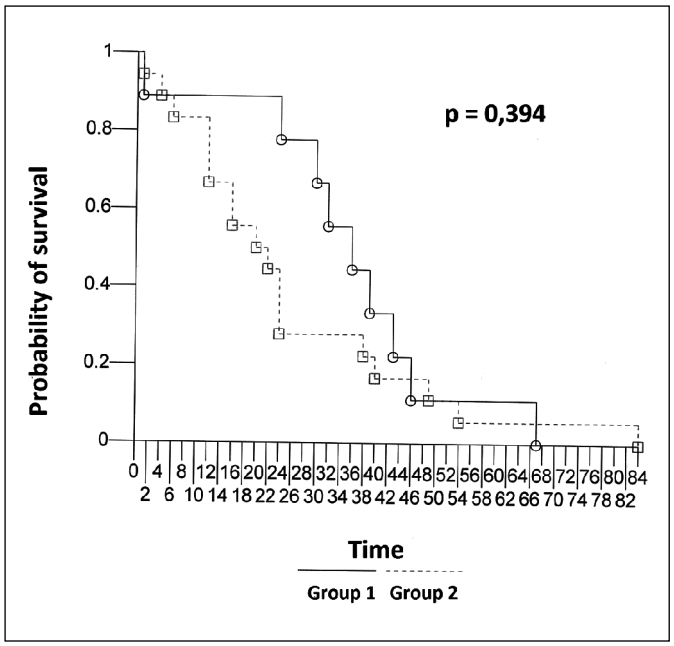

Fig.: 2

tion and within the neoplasm, with a peritumoural prevalence of sub-populations. Ishigami et al. [13] showed that higher clinical aggressiveness is linked to the presence of a high number of tumour-associated macrophages (TAM), regardless of location. Leek et al. [16] have shown a direct relationship between TAM and neoangiogenesis in patients with breast cancer, with reduced disease-free and overall survivals, suggesting CD68+ as an independent prognostic factor. Therefore, the aggressive behaviour of gastric cancer could be attributed to the effect of angiogenic TAM, as evidenced by the microvessels within the tumour [13,17]. In addition, an increased secretion of immunosuppressive cytokines by TAM may also indirectly affect the action of cytotoxic T cells, by altering the transduction signal of the antitumour immune response caused by the T cells themselves. The β-catenin is a subunit of the cadherin protein complex. This protein is important for stabilization of the cytoskeleton, stability of intercellular junctions, and for the signalling pathway called wingless/Wnt. In relation to the latter, the gene coding for -catenin is considered an oncogene. The contact between the cells of nonspecific immunity (macrophages, NK cells, neutrophils) and those of specific immunity (T helperand cytotoxic T lymphocytes, B lymphocytes, and plasma cells) represent a recurring ultra structural picture at level of the lympho plasmacytic tumour infiltrate, in particular in gastric cancer, which suggests the existence of an intense intercellular interaction, through which leukocytes send and receive regulatory messages, thus polarizing the secretion of cytokines and of other mediators [5,18,19]. This interaction could be important in regulating the immune response of the host against gastric cancer, especially in the initial stages, when the growth of the tumour can still be blocked [20].

Particularly interesting is the role of TAM, which in their phenotype M2 seem to promote tumourigenesis and tumour progression, as mentioned before. In fact, other molecule shave recently also been implicated in the development and progression of gastric cancer, such as L1 cell adhesion molecule (L1CAM), epithelial cell adhesion molecule (EPCAM) [21] and matrix metalloproteinase 9 (MMP-9) [21,22]. α-Tumour Necrosis Factor, produced by activated macrophages, in spite of its own name, seems to be a cytokine through which inflammation promotes the development of tumours, in particular through the promotion of the signal Wnt/β-catenin by suppressing phosphorylation of -catenin. Antibodies anti- α -TNF, already and for a long time used in chronic inflammatory diseases [23], represent a possible therapeutic strategy in cancer [24]. Also suppression of the infiltration of macrophages and their activation by means of anti-inflammatory drugs represent a possible chemoprevention against gastric cancer [25-26]. However, new studies are needed to examine thoroughly the nature of this interaction, which might represent these sential principle for the development of immunotherapy, based on the use of substances specifically stimulating the antitumour immune response.

Conclusion

Our study suggests that a high number of TAM along the margins of the tumour is related to a worse outcome, without reaching statistical significance. This finding consorts with other studies on malignancies in general, showing that a high number of TAM is associated with a high probability of lymph node involvement, deeper tumour infiltration, and more advanced clinical stage. Our study also shows a statistically non-significant trend of tumour-associated macrophages in promoting the expression of β- catenin.

Riassunto

Il carcinoma dello stomaco è la seconda causa di morte per cancro in tutto il mondo. Come altre forme di neoplasia, esso innesca una risposta immunitaria caratterizzata dall'infiltrazione del tessuto tumorale e peritumorale da parte di diversi sottotipi di cellule immunocompetenti. Nel nostro studio è stato osservato che un elevato numero di macrofagi infiltranti i margini della neoplasia è associato ad una peggiore prognosi e ad una aumentata espressione di citochine immunosoppressive con conseguente ridotta attività dei linfociti T citotossici.

References

1. Bang Y.-J, Yalcin S, Roth A, Hitier S, Ter-Ovanesov M, Wu CW, Zalcberg J: *Registry of gastric cancer treatment evaluation (REGATE): I baseline disease characteristics.* Asia-Pac J Clin Oncol, 2014; 10: 38-52. doi:10.1111/ajco.12112.

2. Du C, Wang Y: *The immunoregulatory mechanisms of carcinoma for its survival and development*. J Exp Clin Cancer Res, 2011; 30(1):12. doi:10.1186/1756-9966-30-12.

3. Fiori E, De Cesare A, Galati G, et al.: *Prognostic significance of primary-tumor extension, stage and grade of nuclear differentiation in patients with renal cell carcinoma*. J Exp Clin Cancer Res, 2002; 21(2):229-32.

4. Horiguchi S, Petersson M, Nakazawa T, Kanda M, Zea AH, Ochoa AC, Kiessling R: *Primary chemically induced tumours induce profound immunosuppression concomitant with apoptosis and alterations in signal transduction in T cells and NK cells*. Cancer Res, 1999; 59: 2950-956.

5. Orso G,Seruca R, Roviello F: *Gastric cancer carcinogenesis and tumorprogression*. Ann Ital Chir, 2017; 83(3):172-76.

6. Naito Y, Saito K, Shiiba K, et al.: *CD8+ T cells infiltrated within cancer cell nests as a prognostic factor in human colorectal cancer*. Cancer Res, 1998; 58:3491-494.

7. Sica A: *Role of tumour-associated macrophages in cancer-related inflammation*. Exp Oncol, 2010; 32(3):153-58.

8. Corso G, Marrelli D, Roviello F: *Familial gastric cancer and germline mutations of E-cadherin*. Ann Ital Chir, 2012; 83(3):177-82.

9. Suriano F, Santini D, Perrone G, et al.: *Tumor associated macrophages polarization dictates the efficacy of BCG instillation in non- muscle invasive urothelial bladder cancer*. J Exp Clin Cancer Res, 2013; 32(1):1. doi:10.1186/1756-9966-32-87.

10. Giuliani A, Galati G, Demoro M, Scimò M, Pecorella I, Basso L: *Screening of Helicobacter pylori infection after gastrectomy for cancer or peptic ulcer: Results of a cohort study*. Arch Surg, 2010; 145: 962-67.

11. Clements WM, Wang J, Sarnaik A, et al.: *Catenin mutation is a frequent cause of wnt pathway activation in gastric cancer 1.* 2002; 3503-506.

12. Oshima H, Oshima M, Inaba K, Taketo MM: *Hyperplastic gastric tumours induced by activated macrophages in COX-2/mPGES-1 transgenic mice*. EMBO J, 2004; 23:1669-678.

13. Ishigami S, Natsugoe S, Tokuda K, et al.: *Tumor-associated macrophage (TAM) infiltration in gastric cancer.* Anticancer Res, 2003; 23(5A):4079-83.

14. Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma VM: *Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer*. J Pathol, 1997; 182: 318-24.

15. Ben-Baruch: *Inflammation-associated immune suppression in cancer: the roles played by cytokines, chemokines and additional mediators*. Semin Cancer Biol, 2006; 16:38-52.

16. Leek RD, Lewis CE, Whitehouse R, Greenall M, Clarke J, Harris AL: *Association of macrophage infiltration with angiogenesis and prognosis in invasive breast carcinoma*. Cancer Res, 1996; 56: 4625-629.

17. Maeda K, Kang SM, Onoda N, et al.: *Vascular endothelial growth factor expression in preoperative biopsy specimens correlates with disease recurrence in patients with early gastric carcinoma*. Cancer, 1999; 86(4):566-71.

18. Kim SY, Park C, Kim H, et al.: *Deregulation of immune response genes in patients with epstein-barr virus- associated gastric cancer and outcomes*. Gastroenterology, 2015; 148(1):137-47.

19. Kamoshida G, Matsuda A, Miura R. et al.: *Potentiation of tumor cell invasion by co-culture with monocytes accompanying enhanced production of matrix metalloproteinase and fibronectin*. Clin Exp Metastasis, 2013; 30(3):289-97.

20. Rigoli L, Inferrera C: *Prognostic value of intratumoral neutrophils in advanced gastric carcinoma in a high- risk area in northern italy.* Mod Pathol, 2002; 15(8):831-37.

21. Wang Y, Li L, Zhao Z, Wang Y, Ye Z, Tao H.: *L1 and epithelial cell adhesion molecules associated with gastric cancer progression and prognosis in examination of specimens from 601 patients2013:1-11*. Clin Cancer Re, 2013; 16;32:66.

22. Zhang, Q. et al.: *Clinicopathological correlation of keratinocyte growth factor and matrix metalloproteinase-9 expression in human gastric cancer*. Tumori, 2015; 101:566-71.

23. Shanahan JC, St Clair W: *Tumor necrosis factor-alpha blockade: A novel therapy for rheumatic disease*. Clin Immunol, 2002; 103(3 Pt 1):231-42.

24. Wang B, Xu D, Yu X, Ding T, Rao H, Zhan Y: *Association of intra-tumoral infiltrating macrophages and regulatory t cells is an independent prognostic factor in gastric cancer after radical resection.* 2593. Ann Surg Oncol, 2011; 18(9):2585-593.

25. Caporale A, Cosenza UM, Giuliani A, et al.: *Surgical strategy in gastric cancer in aged patients.* G Chir, 1997; 18(1-2):36-40.

26. Fujiwara Y, Omori T, Demura K, et al.: *A multidisciplinary approach for advanced gastric cancer with paraaortic lymph node metastasis.* Anticancer Res, 2015; 35(12):6739-745.