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# Circulating macrophage colony stimulating factor as a marker of tumour progression

## Abstract

Tumour expression of the macrophage colony stimulating factor (CSF-1 or MCSF) has been associated with an adverse prognosis in breast cancer, through an effect on the promotion of metastasis. The aim of the present study was to evaluate the clinical relevance of high circulating CSF-1 levels in patients with newly diagnosed breast tumours and correlate CSF-1 with clinico-pathological parameters. A secondary aim was to also measure CSF-1 in patients with other tumour types and at different stages of disease. Using a commercially available

ELISA, pre-treatment plasma levels of CSF-1 were assessed, in 471 consecutive patients diagnosed with breast tumours, in 70 patients with newly diagnosed cancer of the head & neck, in 32 men with prostate cancer metastatic to bone and in 39 women with advanced metastatic breast cancer. Mean CSF-1 levels were significantly higher in patients with locally advanced ($p < .015$) or metastatic breast tumours ($p < .048$) and in a group of primary breast cancer patients ($n = 26$) selected for intensive chemotherapy because of multiple adverse tumour characteristics ($p < .0002$). Mean CSF-1 was also higher in patients younger than 35 years ($p < .02$) and in post-menopausal patients ($p < .03$). There was no significant association with tumour histologic type, grade, or other individual histopathologic parameters. No significant association was found between pre-treatment CSF-1 and overall/relapse free survival. Median CSF-1 levels were dramatically higher in patients with newly diagnosed tumours of the head & neck (604 pg/ml), in men with prostate cancer metastatic to bone (627 pg/ml) and women with advanced metastatic breast cancer (867 pg/ml) than those seen in patients with newly diagnosed breast tumours (334 pg/ml). Our data support the hypothesis that CSF-1 may play a functional role in tumour progression to metastasis as has previously been reported in animal models.

## Full text

### INTRODUCTION

Colony stimulating factor is a polypeptide growth factor which regulates the survival, proliferation and differentiation of mononuclear phagocytes [1]. Synthesized by many different cell types including fibroblasts, bone marrow stromal cells, lymphocytes and activated macrophages, CSF-1 acts through a high affinity tyrosine kinase receptor encoded by the c-fms proto-oncogene [2], exerting chemotactic effects on precursors of the myeloid lineage, and committing their differentiation into macrophages whilst suppressing dendritic cell differentiation and function [3].

Aside from physiologic production, CSF-1, with or without its receptor c-fms, is also expressed by a variety of human neoplasms including breast [4-6, 9], ovarian [7-10] and endometrial carcinomas [10-12]. Tumours containing a high percentage of CSF-1 expressing cells have been shown to be extensively infiltrated by macrophages, to be clinically aggressive and to be strongly associated with an adverse prognosis [13-16]. Immunohistochemical studies of

breast cancer specimens have shown CSF-1 expression to be higher in invasive as opposed to pre-invasive lesions, suggesting a role for CSF-1 in tumour progression [13]. Moreover, in a pre-clinical mouse mammary tumour model, CSF-1 was demonstrated to act as a promoter of progression to the late stages of carcinoma and the development of metastases, an effect possibly mediated through matrix degrading proteinases produced by the macrophage infiltrate [17].

The aim of this study was to measure circulating CSF-1 in patients with pre-invasive and invasive breast tumours and to correlate plasma concentrations of CSF-1 with clinico-pathologic parameters. A secondary aim was to evaluate the prognostic value of pre-treatment plasma concentrations of CSF-1. Finally, a corroborative study was undertaken to assess circulating CSF-1 levels in patients with other tumour types and at differing stages of tumour progression.

## METHODS

### *Patients*

Clinical information and plasma samples were collected prospectively from 471 consecutive, unselected women with pre-invasive and invasive breast carcinoma diagnosed and treated at the Institut Curie, France between December 1994 and January 1996. Clinico-pathologic data including surgical stage, tumour grade and histologic features were extracted from hospital records while additional epidemiological data including age and menopausal status were also compiled for each patient. Mean and median age of the cohort was 54 years (range 23-85). Twenty-three (5%) were less than 35 years old and 207 (44%) were pre-menopausal.

### *Clinical management*

The diagnosis of breast pathology was established in all cases by tissue biopsy. Tumour classification and staging were in accordance with the International Union Against Cancer tumour-node-metastasis (UICC-TNM) classification. Treatment was administered according to the breast cancer treatment protocol of the host institute. Initial treatment in 315 patients was surgery, 133 received neo-adjuvant chemotherapy prior to surgery and the remaining 23 primary radiotherapy. Twenty-six patients with tumours possessing multiple adverse

histologic features (T2 or greater, rapidly proliferative, oestrogen receptor negative) were recruited to a trial of intensive neoadjuvant chemotherapy. All patients with invasive tumours received further treatment, including hormone therapy, according to institutional protocol.

### *Tumour characteristics*

Tumour was pre-invasive in 26 cases (5.5%) and these patients were used as controls, T1 in 156 (33.1%), T2 in 190 (40.3%), T3 in 66 (14%) and T4 in 27 (5.7%). Of those who had nodal status assessed, 208 (67%) had node negative disease and 99 (33%) node positive. Twenty-seven (5.5%) patients had biopsy proven metastatic disease upon first presentation. Three hundred and twenty-eight patients (69.6%) had oestrogen receptor positive tumours. Histological type in 369 cases (78.3%) was infiltrating ductal carcinoma, in a further 51 (11%) it was infiltrating lobular carcinoma. Tumour grade, as assessed according to the criteria of Scarff Bloom and Richardson was I in 18%, II in 48% and III in 22%. It was not assessed in 12% of cases. Table 1 gives an overview of patient and tumour characteristics and initial treatment modality.

### *Follow up*

After primary and adjuvant treatment, patients were followed by means of routine check-up at the Institut Curie. Radiographic studies were performed only where clinically indicated. Recurrences were defined as the first documented evidence of new disease manifestations in the loco-regional area, in the contra-lateral breast, at distant sites or in a combination of these areas. The RFS and the OS were calculated as the time from diagnosis to the date of first recurrence or death. The follow-up time for patients without documented recurrences or death was calculated as the time from diagnosis to the last clinical examination (last follow-up date October 2000). Patients lost to follow-up were defined as those who had not attended for review within 12 months and for whom no further follow-up data could be obtained.

### *Plasma CSF-1 assay*

Ten millilitres of peripheral venous blood were taken from patients prior to initiation of treatment as part of routine haematological analysis. Blood was collected into a potassium EDTA tube, centrifuged at 1,500 rpm for 15 min, and

stored at - 80° C until examination. For the measurement of plasma CSF-1, a commercially available ELISA kit was used (Quantikine Human M-CSF Immunoassay; R&D Systems, Minneapolis, MN). Duplicate samples were assessed for each patient. The manufacturer claims a sensitivity of < 9 pg/ml and intra-assay variability of 3.4% at a M-CSF concentration of 227 pg/ml. Immunoassays were performed following the manufacturers guidelines. The assay does not exhibit cross-reactivity with a series of cytokines and growth factors.

### *Statistical analysis*

Because of the skewed distribution of plasma concentrations of CSF-1, median and range of plasma concentrations are given. Comparative statistical tests were by chi-squared analysis, as well as by non-parametric testing using BMDP software. Correction for small numbers was by likelihood ratio test and for non-parametric tests by Kruskall-Wallis. Survival data were determined by Mantel-Cox analysis. The results were analysed for the end point of disease free and overall survival. Patients lost to follow up remained in the final analysis and were censored on the date of the last visit to the clinic or on the last date seen by a corresponding physician outside the institute.

### *CSF-1 in other tumour types and stages*

In a bid to corroborate the initial study findings, circulating plasma CSF-1 levels were further assessed in a series of 70 consecutive patients with newly diagnosed squamous tumours of the head & neck, 32 ambulant men with prostate carcinoma metastatic to bone and a cohort of 39 women with advanced, metastatic breast tumours requiring hospital admission for symptom control.

## RESULTS

### *Plasma concentrations of CSF-1 in patients with newly diagnosed breast tumours*

A broad range of circulating CSF-1 levels were found, ranging from 33 to 2,564 pg/ml with median and mean values at 334 pg/ml and 394.1 pg/ml respectively. Figure 1 depicts the distribution of CSF-1 values obtained. Overall, the median

CSF-1 value in patients with invasive cancer (334 pg/ml) was not significantly higher than that in the control patients with pre-invasive disease (310 pg/ml) or in previously reported healthy controls (364 ± 69 pg/ml) [18]. Statistically significant associations were seen between CSF-1 and age less than 35 years (Kruskall-Wallis, $p < .02$) and post-menopausal status (Kruskall-Wallis, $p < .02$).

### *Correlation of plasma concentrations of CSF-1 with tumour stage and pathological characteristics*

When plasma concentrations of CSF-1 were grouped by tumour stage, a significant association was observed between circulating CSF-1 and locally advanced or inflammatory primary tumours (T1 *versus* T2 *versus* T3 *versus* T4, Kruskall-Wallis, $p < .015$) and also between CSF-1 and the presence of metastatic disease at diagnosis (Kruskall-Wallis, $p < .048$). No significant correlation was found between CSF-1 and steroid receptor values (Kruskall-Wallis, $p = .9$), histologic grade (Kruskall-Wallis, $p = .29$) or type (Kruskall-Wallis, $p = .18$). However, a significant elevation in circulating CSF-1 levels (Kruskall-Wallis, $p = .0002$) was seen in a small group of patients ($n = 26$) pre-selected for intensive neoadjuvant chemotherapy on the basis of multiple adverse pathologic features including large tumour size, rapid proliferative rate and oestrogen receptor negativity. Table 2 demonstrates the correlation between mean pre-treatment CSF-1 levels and clinico-pathologic characteristics

### *Circulating CSF-1 in other tumour types*

In an attempt to substantiate the correlation obtained in the prospective population between CSF-1 and locally advanced or metastatic disease, we assayed circulating plasma CSF-1 levels in other carefully selected patient groups. Firstly, 70 patients with newly diagnosed primary squamous tumours of the head & neck were screened before initiation of treatment. This tumour type was chosen as it is typically diagnosed at a locally advanced stage. Median CSF-1 in this cohort was 604 pg/ml (range 71-2,200 pg/ml, mean 720 pg/ml) Secondly, values were assessed in 32 ambulant men with bone metastases from prostate carcinoma, yielding a median CSF-1 value of 627 pg/ml (range 59-4,711 pg/ml, mean 1,123 pg/ml). Finally, 39 women with advanced metastatic breast cancer requiring hospital admission for symptom relief had values assessed. These had a median CSF-1 value of 865 pg/ml (range 126-5,790 pg/ml, mean 1,240 pg/ml).

Figure 2 depicts the distribution of these values in comparison to those obtained prospectively from the patients with newly diagnosed breast tumours.

### *Clinical outcomes*

As a precise cut-off level for plasma CSF-1 remains to be defined, patients were classified into groups based on the level of initial CSF-1 for the purpose of analysis. Median and twice median plasma values were chosen as cut-off points, resulting in the following classes. Zero to 349 pg/ml (n = 255, 54.2%) 350 to 699 pg/ml (n = 183, 38.8%) and > 700 pg/ml (n = 33, 7%). At a median follow up of 67 months (range 5-84 months), the overall and relapse-free survival were 84.5% and 78.7% respectively, with a total of 71 deaths recorded. Twenty-eight patients (5.9%) have been lost to follow up, all of whom were included in the survival analysis. In the total patient population, no statistically significant differences in overall survival were seen between those patients with CSF-1 levels < 350 pg/ml, greater than 350 and less than 700 pg/ml, and > 700 pg/ml (Table 3) (p = 0.87), with approximately equal ratios of patients remaining alive in each group. Thity-seven patients are alive with evidence of recurrent disease. After censoring those with metastatic disease at diagnosis from the analysis (n = 27), no differences were detected in relapse-free survival according to initial CSF-1 levels (p = .19).

## DISCUSSION

In this study of patients with newly diagnosed breast tumours, we found circulating plasma CSF-1 levels to be elevated in patients with regionally advanced disease and distant metastases as compared to patients with localised tumours. Moreover, in a corroborative study, we also demonstrated significantly elevated CSF-1 levels in women with end-stage breast cancer. Lin *et al.* [17] crossed a transgenic mouse susceptible to mammary cancer with mice containing a recessive null mutation in the CSF-1 gene before subsequently inducing transgenic CSF-1 expression in the mammary epithelium. Using this model, they were able to demonstrate that while CSF-1 expression does not affect initiation and growth of primary tumours, it does promote acceleration to the late stages of carcinoma and the development of metastases. When our results are considered in the context of these findings, they support a role for CSF-1 in breast cancer progression.

Moreover, the results obtained in men with bone metastases from prostate cancer and in patients with newly diagnosed head & neck tumours, a tumour type which typically presents with loco-regionally advanced disease, suggest that the effects mediated by this growth factor may equally be important in other tumour types. This is concordant with data showing CSF-1 to be a useful tumour marker in ovarian cancer [19], again a tumour type which typically presents at an advanced stage.

How is this effect mediated? Tumour CSF-1 expression is associated with extensive macrophage infiltration both in animal [17, 20] and human tumours [13, 21]. While the biological role and clinical significance of macrophages in tumour tissue is still unclear [22] they have the potential to exert beneficial anti-tumour effects through the secretion of cytotoxic substances and presentation of tumour associated antigens to lymphocyte [23]. However in pre-clinical models, although transgenic expression of CSF-1 induced macrophage infiltration [17, 20] there was no resultant suppression of tumour growth. This has led to the hypothesis that CSF-1 favours tumour progression through the attraction and differentiation of macrophages which promote angiogenesis and the remodelling of tumour stroma rather than exerting cytotoxic activity [5, 17, 21, 24]. In patients with small primary breast tumours amenable to surgery - the majority of our patients -, it is possible that secreted CSF-1 has not yet recruited sufficient macrophages to produce such an effect. This could explain the lack of significant correlation between circulating CSF-1 and survival.

In addition, it has previously been demonstrated that activation of the CSF-1 receptor c-fms by its cognate ligand dramatically increases the tumorigenicity and invasive potential of mammary tumour epithelial cells [25] and lung cancer cells [26] through an autocrine mechanism. Finally, CSF-1 has been implicated in tumour evasion of the host immune response. Dendritic cells (DCs) play an integral role in the initiation of a specific T-cell response by processing tumour associated antigens and presenting them to sensitised T lymphocytes [27]. It has been demonstrated that tumour culture supernatants contain elements which can inhibit the functional maturation of DCs [28-30] and that dendritic cells taken from patients with a variety of solid tumours have an impaired ability to stimulate allogeneic T-lymphocytes [31-33]. In this context, Menetrier-Caux *et al.* [30] demonstrated that CSF-1 produced by renal cell carcinoma cell lines inhibited the differentiation of DCs from $CD34^+$ progenitor cells, instead resulting in monocytic cells with a potent phagocytic activity but lacking antigen

presenting function. We were further able to show that the CSF-1 induced reduction in allostimulatory function may be mediated by an effect on MHC class II traffic [34].

In the present study, while no meaningful relationship was detected between circulating levels of CSF-1 and histologic type, grade or other individual histologic parameters, we did find a significant elevation in CSF-1 levels in a small group of patients pre-selected for intensive neoadjuvant chemotherapy on the basis of multiple adverse pathologic features, indicating that it may also be a marker of tumour de-differentiation. Further studies will be required to support this hypothesis. The higher circulating CSF-1 concentrations in patients younger than 35 years is presumably related to its role in the regulation of the menstrual cycle [35, 36]. Similarly, the relatively higher levels in post-menopausal patients are coherent with its role in the catabolic modifications and osteoporosis associated with oestrogen deficiency [37, 38]. Indeed elevated CSF-1 levels have previously been reported in an elderly population without overt malignant disease [39].

The fact that the median CSF-1 in patients with newly diagnosed breast tumours was no higher than control suggests that a plasma CSF-1 assay may not accurately reflect tissue activity in patients with primary breast tumours. We have shown that circulating CSF-1 is related to tumour volume, however, many of the breast tumours in our series were screen detected and relatively small, therefore, even if over-expressing CSF-1, were not secreting sufficient cytokine to provoke a rise in plasma levels. In order to produce a significant elevation in plasma levels, a tumour must secrete sufficient CSF-1 to allow spill over into the circulation. Moreover, upon reaching the circulation, CSF-1 has a half-life of approximately 10 min, being efficiently cleared by high affinity CSF-1 receptors on macrophages [1], thus it must be synthesized continuously in order to maintain stable circulating levels.

If as this study suggests, CSF-1 plays a role in the progression of cancer and the development of metastatic disease, we need to evaluate means by which we can easily and reliably assess tumour CSF-1 expression. A more valid indication might be achieved by measuring tumour cytosol CSF-1 expression as was demonstrated for VEGF [40], however this method would not discriminate between the CSF-1 produced by the tumour itself and that produced by tumour infiltrating inflammatory cells. Routine assessment for expression of CSF-1 and

its receptor c-fms in the tumour micro-environment by either polymerase chain reaction or immunohistochemistry remain to be prospectively evaluated, although evidence exists to support the use of the latter as a prognostic test both in breast cancer [13] and in other tumour types [12, 15, 16].

CONCLUSION

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## References

1. Praloran V. 1991. Structure, biosynthesis and biological roles of monocyte-macrophage colony stimulating factor (CSF-1 or M-CSF). (Review) *Nouv. Rev. Fr. Haematol.* 33: 323.

2. Sherr C J, Rettenmier C W, Sacca R, Roussel M F, Look A T, Stanley E R. 1985. The c-fms proto-oncogene product is related to the receptor for the mononuclear phagocyte growth factor, CSF-1. *Cell* 41: 665.

3. Hausser G, Ludewig B, Gelderblom H R, Tsunetsugu-Yokota Y, Akagawa K, Meyerhans A. 1997. Monocyte-derived dendritic cells represent a transient stage of differentiation in the myeloid lineage. *Immunobiology* 197: 534.

4. Tang R, Beuvon F, Ojeda M, Mosseri V, Pouillart P, Scholl S M. 1992. M-CSF (monocyte colony stimulating factor) and M-CSF receptor expression by breast tumour cells: M-CSF mediated recruitment of tumour infiltrating monocytes? *J. Cell Biochem.* 50: 350.

5. Scholl S M, Crocker P, Tang R, Pouillart P, Pollard J W. 1993. Is CSF-1 a key mediator of breast cancer invasion and metastasis? (Review) *Mol. Carcinog.* 7: 207.

6. Kacinski B M, Scata K A, Carter D, Yee L D, Sapi E, King B L, Chambers S K, Jones M A, Pirro M H, Stanley E R, Rohrschneider L. 1991. FMS (CSF-1 receptor) and CSF-1 transcripts and protein are expressed by human breast carcinomas *in vivo* and *in vitro. Oncogene* 6: 941.

7. Kacinski B, Stanley E R, Carter D, Chambers J T, Chambers S K, Kohorn E I, Schwarz P E. 1989. Circulating levels of CSF-1 (M-CSF) a lymphohematopoetic cytokine may be a useful marker of disease status in patients with malignant ovarian neoplasms. *Int. J. Radiat. Oncol. Biol. Phys.* 17: 159.

8. Kacinski B M, Carter D, Mittal K, Yee L D, Scata K A, Donofrio L, Chambers S K, Wang K I, Yang-Feng T, Rohrschneider L R, Rothwell VM. 1990. Ovarian adenocarcinomas express fms-complementary transcripts and fms antigen, often with coexpression of CSF-1. *Am. J. Pathol.* 137: 135.

9. Ramakrishnan S, Xu F J, Brandt S J, Niedel J E, Bast R C Jr, Brown E L. 1989. Constitutive production of macrophage colony-stimulating factor by human ovarian and breast cancer cell lines. *J. Clin. Invest.* 83: 921.

10. Baiocchi G, Kavanagh J J, Talpaz M, Wharton J T, Gutterman J U, Kuizrock R. 1991. Expression of the macrophage colony-stimulating factor and its receptor in gynecologic malignancies. *Cancer* 67: 990.

11. Kacinski B M, Carter D, Mittal K, Kohorn E I, Bloodgood R S, Donohue J, Donofrio L, Edwards R, Schwarz P E, Chambers J T, Chambers S K. 1988. High level expression of fms proto-oncogene is observed in clinically aggressive human endometrial adenocarcinomas. *Int. J. Radiat. Oncol. Biol. Phys.* 15: 823.

12. Kacinski B M, Chambers S K, Stanley E R, Carter D, Tseng P, Scata K A, Chang D H, Pirro M H, Nguyen J T, Ariza A. 1990. The cytokine CSF-1 (M-CSF) expressed by endometrial carcinomas *in vivo* and *in vitro*, may also be a circulating tumour marker of neoplastic disease activity in endometrial carcinoma patients. *Int. J. Radiat. Oncol. Biol. Phys.* 19: 619.

13. Scholl S M, Pallud C, Beuvon F, Hacene K, Stanley E R, Rohrschneider L, Tang R, Pouillart P, Lidereau P. 1994. Anti-colony-stimulating factor-1 antibody staining in primary breast adenocarcinomas correlates with marked inflammatory cell infiltrates and prognosis. *J. Natl. Cancer Inst.* 86: 120.

14. Tang R P, Kacinski B, Validire P, Beuvon F, Sastre X, Benoit P, de la Rochefordiere A, Mosseri V, Pouillart P, Scholl S. 1990. Oncogene amplification correlates with dense lymphocytic infiltration in human breast cancers: a role for hemopoeitic growth factor release by tumour cells? *J. Cell Biochem.* 44: 189.

15. Chambers S K, Kacinski B M, Ivins C M, Carcangiu M L. 1997. Overexpression of epithelial macrophage colony stimulating factor (CSF-1) and CSF-1 receptor: a poor prognostic factor in epithelial ovarian cancer, contrasted with a protective effect of stromal CSF-1. *Clin. Cancer Res.* 3: 999.

16. Smith H O, Anderson P S, Kuo D Y, Goldberg G L, de Victoria C L, Boocock C A, Jones J G, Runowicz C D, Stanley E R, Pollard J W. 1995. The role of colony-stimulating factor-1 and its receptor in the etiopathogenesis of endometrial adenocarcinoma. *Clin. Cancer Res.* 1: 313.

17. Lin E Y, Nguyen A V, Russell R G, Pollard J W. 2001. Colony-stimulating factor 1 promotes progression of mammary tumours to malignancy. *J. Exp. Med.* 193: 727.

18. Yong K, Salooja N, Donahue R E, Hegde U, Linch D C. 1992. Human macrophage colony stimulating factor levels are elevated in pregnancy and in immune thrombocytopenia. *Blood* 80: 2897.

19. Scholl S M, Bascou C H, Mosseri V, Olivares R, Magdelenat H, Dorval T, Palangie T, Validire P, Pouillart P, Stanley E R. 1994. Circulating levels of colony-stimulating factor 1 as a prognostic indicator in 82 patients with epithelial ovarian cancer. *Br. J. Cancer* 69: 342.

20. Dorsch M, Hock H, Kunzendorf U, Diamantstein T, Blankenstein T. 1993. Macrophage colony-stimulating factor gene transfer into tumor cells induces macrophage infiltration but not tumor suppression. *Eur. J. Imm.* 23: 186-90.

21. Hemmerlein B, Markus A, Wehner M, Kugler A, Zschunke F, Radzum H J. 2000. Expression of acute and late-stage inflammatory antigens, c-fms, CSF-1 and human monocystine esterase 1, in tumour-associated macrophages of renal cell carcinomas. *Cancer Immunol. Immunother.* 49: 485.

22. Elgert K D, Alleva D G, Mullins D W. 1998. Tumour induced immune dysfunction: the macrophage connection. (Review) *J. Leukoc. Biol.* 64: 275.

23. Bonta I L, Ben-Efraim S. 1993. Involvement of inflammatory mediators in macrophage antitumour activity. (Review) *J. Leukoc. Biol.* 54: 613.

24. Dougherty S T, Eaves C J, McBride W H, Dougherty G J. 1997. Role of macrophage colony stimulating factor in regulating the accumulation and phenotype of tumour associated macrophages. *Cancer Immunol. Immunother.* 44: 165.

25. Sapi E, Flick M B, Rodov S, Gilmore-Hebert M, Kelley M, Rockwell S, Kacinski B M. 1996. Independent regulation of invasion and anchorage independent growth by different autophosphorylation sites of the macrophage colony-stimulating factor 1 receptor. *Cancer Res.* 56: 5704.

26. Pei X H, Nakanishi Y, Takayama K, Bai F, Hara N. 1999. Granulocyte, granulocyte-macrophage, and macrophage colony stimulating factors can stimulate the invasive capacity of human lung cancer cells. *Br. J. Cancer* 79: 40.

27. Watts C. 1997. Capture and processing of exogenous antigens for presentation on MHC molecules. (Review) *Annu. Rev. Immunol.* 15: 821.

28. Gabrilovich D I, Chen H L, Girgis K R, Cunningham H T, Meny G M, Nadaf S, Kavanaugh D, Carbone D P. 1996. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. *Nat. Med.* 2: 1096.

29. Steinbrink K, Wolfl M, Jonuleit H, Knop J, Enk A H. 1997. Induction of tolerance by IL-10 treated dendritic cells. *J. Immunol.* 159: 4772.

30. Menetrier-Caux C, Montmain G, Dieu M C, Bain C, Favrot M C, Caux C, Blay J Y. 1998. Inhibition of the differentiation of dendritic cells from $CD34^+$ progenitors by tumour cells: role of interkeukin-6 and macrophage colony stimulating factor. *Blood* 92: 4778.

31. Gabrilovich D I, Corak J, Ciernik I F, Kavanaugh D, Carbone D P. 1997. Decreased antigen presentation by dendritic cells in patients with breast cancer. *Clin. Cancer Res.* 3: 1483.

32. Ishida T, Oyama T, Carbone D P, Gabrilovich D I. 1998. Defective function of Langerhans cells in tumour-bearing animals is the result of defective maturation from hemopoietic progenitors. *J. Immunol.* 161: 4842.

33. Almand B, Resser J R, Lindman B, Nadaf S, Clark J I, Kwon E D, Carbone D P, Gabrilovich D I. 2000. Clinical significance of defective dendritic cell differentiation in cancer. *Clin. Cancer Res.* 6: 1755.

34. Baron C, Raposo G, Scholl S M, Bausinger H, Tenza D, Bohbot A, Pouillart P, Goud B, Hanau D, Salamero J. 2000. Modulation of MHC class II transport and lysosome distribution by macrophage-colony stimulating factor in human dendritic cells derived from monocytes. *J. Cell Sci.* 114: 999-1010.

35. Shinetugs B, Runesson E, Bonello N P, Brannstrom M, Norman R J. 1999. Colony stimulating factor-1 concentrations in blood and follicular fluid during the human menstrual cycle and ovarian stimulation: possible role in the ovulatory process. *Hum. Reprod.* 14: 1302.

36. Pampfer S, Tabibzadeh S, Chuan F C, Pollard J W. 1991. Expression of colony-stimulating factor-1 (CSF-1) messenger RNA in human endometrial glands during the menstrual cycle: molecular cloning of a novel transcript that predicts a cell surface form of CSF-1. *Mol. Endocrinol.* 5: 1931.

37. Kimble R B, Srivastava S, Ross F P, Matayoshi A, Pacifici R. 1996. Estrogen deficiency increases the ability of stromal cells to support murine osteoclastogenesis *via* an interleukin-land tumor necrosis factor-mediated stimulation of macrophage colony-stimulating factor production. *J. Biol. Chem.* 271: 28890.

38. Srivastava S, Weitzmann M N, Kimble R B, Rizzo M, Zahner M, Milbrandt J, Ross F P, Pacifici R. 1998. Estrogen blocks M-CSF gene expression and osteoclast formation by regulating phosphorylation of Egr-1 and its interaction with Sp-1. *J. Clin. Invest.* 102: 1850.

39. Hasegawa Y, Sawada M, Ozaki N, Inagaki T, Suzumura A. 2000. Increased soluble tumour necrosis factor levels in the serum of elderly people. *Gerontology* 46: 185.

40. Linderholm B, Grankvist K, Wilking N, Johansson M, Tavelin B, Henriksson R. 2000. Correlation of vascular endothelial growth factor content with recurrences, survival, and first relapse site in primary node-positive breast carcinoma after adjuvant treatment. *J. Clin. Oncol.* 18: 1423.

## Figures

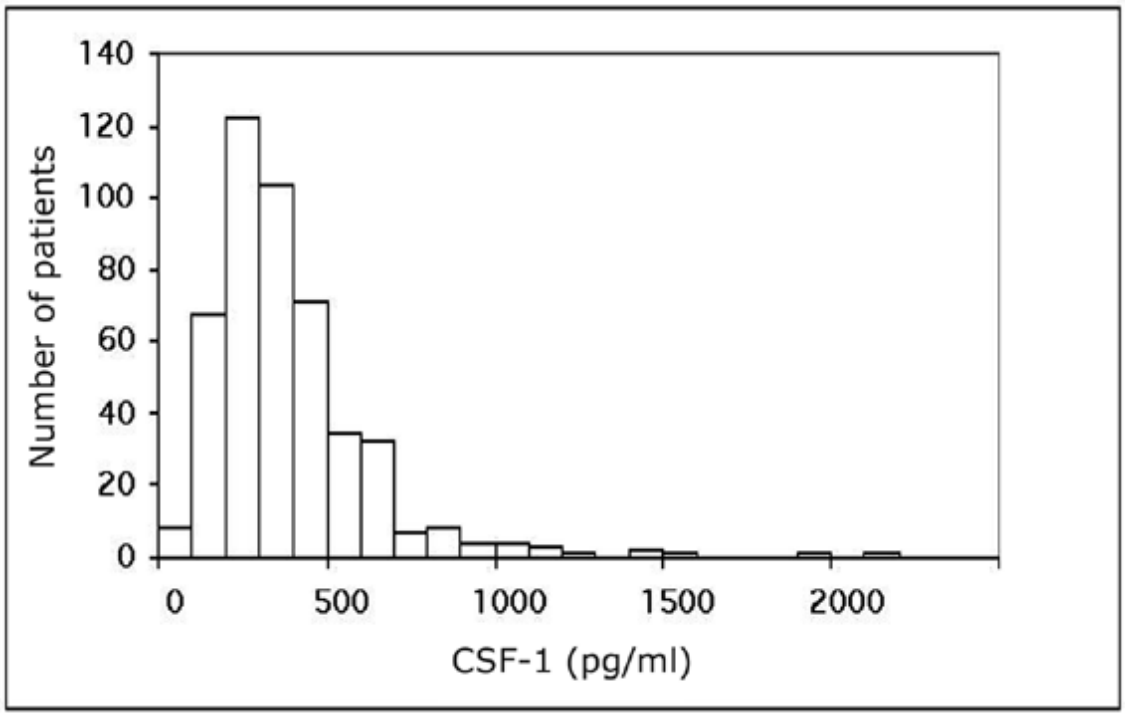



**Figure 1**
**Distribution of circulating CSF-1 levels estimated prospectively in 471 consecutive patients with newly diagnosed breast tumours.** Median 334 pg/ml, range 35-2,564 pg/ml, mean 394.1 pg/ml.

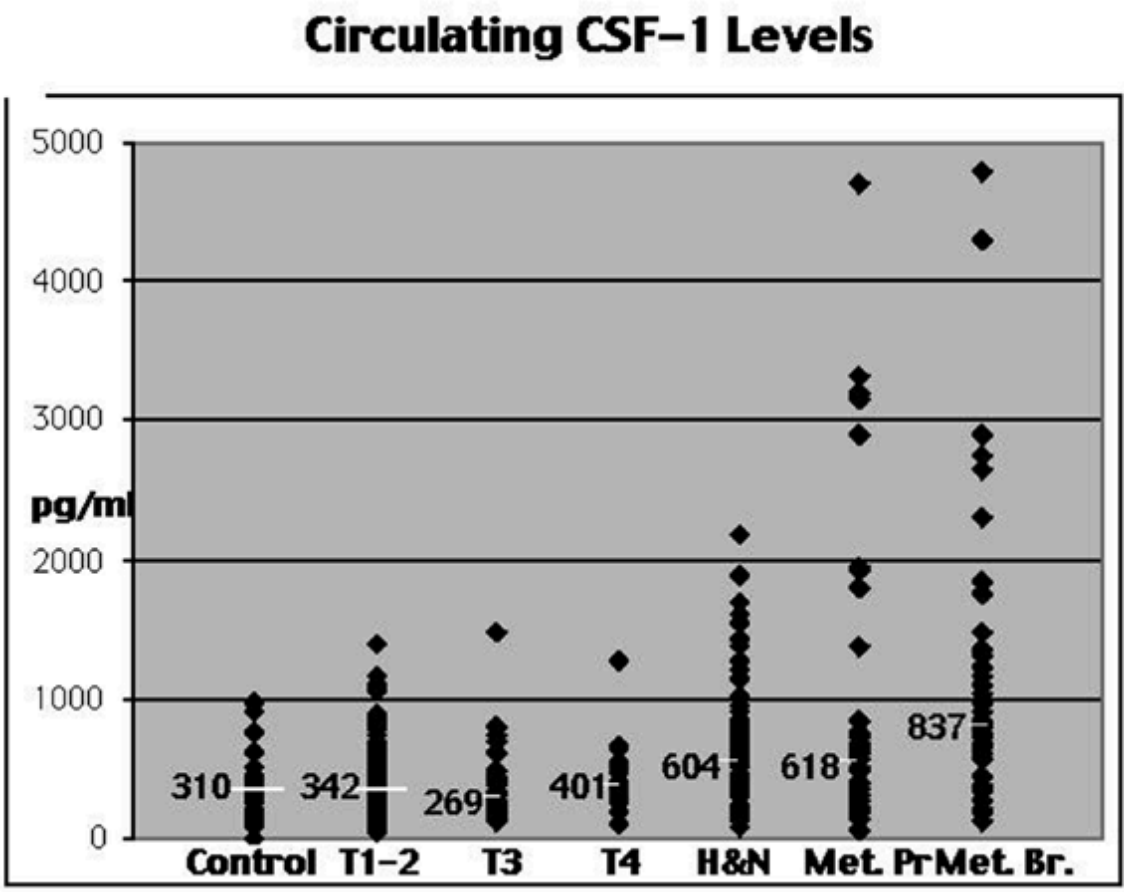



**Figure 2**

**CSF-1 results categorised according to tumour stage and type.** Median values in each group are denoted by horizontal line and numerical value. Annotation: control, pre-invasive tumours; T-T4: prostective breast tumours classified according to size; H&N: pre-treatment tumours of the head & neck; Met. Pr.: prostate cancer metastatic to bone; Adv. Br.: advanced metastatic breast cancer.

**Table 1**
**Characteristics of the patients, the tumors and the initial treatment modality**

| | Patients | |
|---|---|---|
| | Number | % |
| Total | 471 | 100 |
| Age* | | |
| < 35 | 23 | 4.9 |
| > 35-< 55 | 240 | 51 |
| > 55 | 208 | 44.1 |
| Menopausal status | | |
| Pre-menopausal | 228 | 48.4 |
| Post-menopausal | 230 | 48.8 |
| Initial treatment | | |
| Surgery | 315 | 66.9 |
| Chemotherapy | | |
| Intensive** | 26 | 5.5 |
| Standard | 107 | 22.7 |
| Radiotherapy | 23 | 4.9 |
| Tumour size | | |
| Pre-invasive | 26 | 5.5 |
| T1 | 156 | 33.2 |
| T2 | 190 | 40.3 |
| T3 | 66 | 14 |
| T4 | 27 | 5.7 |
| Tx | 6 | 1.3 |
| Nodal status | | |
| N0 | 208 | 44.2 |
| N1-3 | 99 | 21 |
| Nx | 164 | 34.8 |
| Distant metastases | | |
| M0 | 444 | 94.3 |
| M1 | 27 | 5.7 |
| Oestrogen receptor | | |
| Positive | 328 | 69.7 |
| Negative | 98 | 20.1 |
| Histopathologic grade | | |
| 1 | 84 | 17.8 |
| 2 | 225 | 47.8 |
| 3 | 106 | 22.5 |
| Not analysed | 56 | 11.9 |
| Histologic type | | |
| Carcinoma *in situ* | 26 | 5.5 |
| Infiltrating ductal | 369 | 78.3 |
| Infiltrating lobular | 51 | 10.8 |
| Other*** | 25 | 5.3 |

* Median age 54 (range 23-85); ** chosen on the basis of multiple adverse pathologic criteria including large tumour size, rapid proliferatan and oestrogen receptor negativity; *** includes squamous, medullary, papillary, tubular and apocrine carcinomas.

**Table 2**
**Correlation between plasma CSF-1 levels and clinico-pathologic characteristics**

| | Mean CSF-1 (pg/ml) | p* |
|---|---|---|
| All patients | 394.1 | |
| Age | | |
| < 35 | 494.4 | 0.02 |
| > 35-< 55 | 370.1 | |
| > 55 | 411.3 | |
| Menopausal status | | |
| Pre-menopausal | 366.9 | 0.03 |
| Post-menopausal | 421.5 | |
| Intensive neoadjuvant Chemotherapy | | |
| Yes | 559.5 | 0.0002 |
| No | 386.4 | |
| Tumour size | | |
| T1 | 361.1 | |
| T2 | 417.8 | |
| T3 | 399.4 | |
| T4 | 444.4 | 0.015 |
| Distant metastases | | |
| No | 391.3 | 0.05 |
| Yes | 446.1 | |
| Oestrogen receptor | | |
| Positive | 396.8 | 0.9 |
| Negative | 393.1 | |
| Histopathologic grade | | |
| 1 | 442 | 0.29 |
| 2 | 388.5 | |
| 3 | 387.2 | |
| Histologic type | | |
| Carcinoma *in situ* | 358.6 | 0.18 |
| Infiltrating ductal | 388.3 | |
| Infiltrating lobular | 356.1 | |

* Kruskall-Wallis test.

**Table 3**
**Correlation of overall survival with initial CSF-1 value***

| Initial CSF-1 (pg/ml) | Number of patients | Deaths observed | Deaths expected | Obs./Exp. ratio | % surviving | P value |
|---|---|---|---|---|---|---|
| < 350 | 255 | 40 | 39.2 | 1.02 | 84.6 | 0.87** |
| > 350-< 700 | 183 | 27 | 26.6 | 1.01 | 84.2 | |
| > 700 | 33 | 4 | 5.1 | 0.78 | 84.9 | |

* Median follow-up 7 months (range 5-84); ** Mantel-Cox analysis.

## Authors

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CSF-1, tumour progression, metastasis, de-differentiation.

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IL-1beta, TNF-alpha, GM-CSF, neuron, mRNA, protein.

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