Sunitinib-Induced Myeloid Lineage Redistribution in Renal Cell Cancer Patients: CD1c⁺ Dendritic Cell Frequency Predicts Progression-Free Survival

Hester van Cruysen, Astrid A.M. van der Veldt, Laura Vroling, Dinja Oosterhoff, Henk J. Broxterman, Rik J. Scheper, Giuseppe Giaccone, John B.A.G. Haanen, Alfons J.M. van den Eertwegh, Epie Boven, Klaas Hoekman, and Tanja D. de Gruijl

Abstract

Purpose: A disturbed myeloid lineage development with abnormally abundant neutrophils and impaired dendritic cell (DC) differentiation may contribute to tumor immune escape. We investigated the effect of sunitinib, a tyrosine kinase inhibitor of fms-like tyrosine kinase-3, KIT, and vascular endothelial growth factor receptors, on myeloid differentiation in renal cell cancer (RCC) patients.

Experimental Design: Twenty-six advanced RCC patients were treated with sunitinib in a 4-week on/2-week off schedule. Enumeration and extensive phenotyping of myeloid subsets in the blood was done at baseline and at weeks 4 and 6 of the first treatment cycle. Baseline patient data were compared with sex- and age-matched healthy donor data.

Results: Baseline frequencies of DC subsets were lower in RCC patients than in healthy donors. After 4 weeks of sunitinib treatment, a generalized decrease in myeloid frequencies was observed. Whereas neutrophils and monocytes, which were both abnormally high at baseline, remained low during the 2-week off period, DC rates recovered, resulting in a normalized myeloid lineage distribution. Subsequent to sunitinib treatment, an increase to high levels of myeloid DC (MDC) subset frequencies relative to other myeloid subsets, was specifically observed in patients experiencing tumor regression. Moreover, high CD1c/BDCA-1⁺ MDC frequencies were predictive for tumor regression and improved progression-free survival.

Conclusion: The sunitinib-induced myeloid lineage redistribution observed in advanced RCC patients is consistent with an improved immunestatus. Immunologic recovery may contribute to clinical efficacy as suggested by the finding of highly increased MDC frequencies relative to other myeloid subsets in patients with tumor regression.

Authors' Affiliations: 1Medical Oncology, VU University Medical Center, Amsterdam, and 3Department of Immunology, the Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands; and 4Medical Oncology Branch, CCR, National Cancer Institute, NIH, Bethesda, Maryland

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Requests for reprints: Tanja D. de Gruijl, VU University Medical Center, Department of Medical Oncology, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands. Phone: 31-20-444-4063; Fax: 31-20-444-4355; E-mail: td.degruijl@vumc.nl.

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One of the major mechanisms of tumors to escape from immunosurveillance is hampered dendritic cell (DC) differentiation (1). In cancer patients, frequencies of circulating DCs are significantly lower compared with those in healthy individuals (2, 3). Accumulation of immature myeloid cells (ImC) and functionally impaired DCs has been documented in blood, tumors, and tumor-draining lymph nodes of cancer patients and found to be a poor prognostic factor (3–5).

Vascular endothelial growth factor (VEGF) can contribute to tumor-induced DC defects in vitro and in vivo (6–8). In cancer patients, an association has been found between high levels of circulating VEGF and increased numbers of circulating ImCs (4) and decreased numbers of more mature DC precursors (9). In gastric and non–small cell lung cancer biopsies, DC density was inversely correlated with intratumoral VEGF levels (10, 11). In a heterogeneous population of advanced cancer patients, inhibition of VEGF signaling with VEGF-Trap, a fusion protein neutralizing VEGF and placental growth factor, was shown to increase the frequency of mature DC precursors in the blood but did not alter frequencies of ImCs (12). Another study examining the DC immune potentiating effects of bevacizumab, a monoclonal antibody against VEGF, showed a decrease in ImCs but no significant increase in mature DC precursors in the blood of cancer patients (13). We previously failed to observe normalizing effects of cediranib (AZD2171), a VEGF receptor tyrosine kinase inhibitor, on mature DC precursors in a heterogeneous group of advanced cancer patients. We did, however, observe a slight decrease in myeloid suppressor cells (MDC) and functionally impaired DCs was documented in blood, tumors, and tumor-draining lymph nodes of cancer patients and found to be a poor prognostic factor (3–5).
In light of the abnormal myeloid lineage differentiation profile in RCC patients and its possible adverse consequences in terms of immune competence, we studied the influence of the broad inhibitory activity of sunitinib on the myeloid blood profile, including PBDCs. Our data show that daily administration of sunitinib for 4 weeks followed by a 2-week rest period results in a normalization of circulating neutrophils and PBDC frequencies relative to other myeloid subsets. In addition, we report an association between a sunitinib-induced tumor regression and an increased frequency of one PBDC subset in particular, the CD1c/BDCA-1+ myeloid DC (MDC)-1 subset.

**Patients and Methods**

**Patients.** Patients with advanced RCC were treated with sunitinib in an expanded access program. Between January 2006 and March 2007, 26 patients were enrolled in the DC monitoring studies. Patients received sunitinib 50 mg per day p.o. during the first 4 wk, followed by 2 wk of rest. This 6-wk time period was defined as one treatment cycle. Sunitinib has a half-life ranging from 41 to 68 h (27). Leukocytes and their differential were quantitated by the use of CELL-DYN (Abbott). Hematologic adverse events were graded using the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 3.0. Efficacy of sunitinib was determined after every two or three cycles using one-dimensional measurements on computed tomography scans. At baseline, the sum of the largest diameters of appointed target tumor lesions was calculated and was compared with the sum calculated in follow-up scans. A 20% decrease of the sum of the target lesions was considered regression, and a 20% increase of the sum or clear clinical evidence of progressive disease was considered progression. When these criteria were not met, responses were considered stable. Patients continued on sunitinib treatment for the duration of clinical benefit. Progression-free survival (PFS) was the time between the first day of sunitinib and the date of evidence for progression. For PFS analysis, data collection was closed on January 1st, 2008.

The DC monitoring study was approved by the Medical Ethical Committee of the participating institutes. After obtaining written informed consent, patients were enrolled.

**DC monitoring.** Blood for DC monitoring was drawn at baseline, and 4 and 6 wk after the start of sunitinib treatment. Peripheral blood mononuclear cells (PBMC) were isolated after a density gradient separation by the use of a Vacutainer CPT Cell Preparation Tube (BD), following the manufacturer’s instructions. After isolation, PBMCs were washed twice, and viable cells were counted based on trypan blue exclusion.

Analysis of the ImCs, MSCs, and PBDC subset frequencies (Table 1) and their maturation status was done using four-color staining with antibodies directly conjugated with fluorochromes FITC, PE,
PerCP-Cy5, or APC, followed by flowcytometric analysis of 50 to 150,000 events, using a FACS Calibur and Cellquest fluorescence-activated cell sorting analysis software (BD Biosciences). Monoclonal antibodies against the following markers used were as follows: CD3, CD11c, CD14, CD19, CD56, CD123, HLA-DR (all BD Biosciences), CD40 (Immunotech), and blood DC antigen (BDCA)-1 (i.e., CD1c), BDCA-2, BDCA-3, (all Miltenyi Biotec GmbH). A gate was set at the lymphocyte/mononuclear populations based on the forward and sideward scatter plots to avoid erythrocytes, cell debris, and neutrophil contamination.

ImCs, previously identified as MDC/macrophage precursors in varying stages of differentiation (28), were defined as positive for CD11c, but negative for the lineage (Lin) markers CD3 (T cells), CD14 (monocytes), CD19 (B cells), and CD56 (natural killer cells), as well as for HLA-DR as previously described (Table 1; refs. 3, 4). MSCs were defined as CD14+HLA-DRneg/low cells (Table 1; refs. 3, 14). PBDC frequencies were determined on the basis of expression of BDCA markers (Table 1): DCs belonging to the so-called myeloid DC subset-1 (MDC-1) were identified as CD11chigh, CD19-, CD14-, and BDCA-1/CD1c+; MDC-2 were detected as CD11c+, CD14-, and BDCA-3+ (29); and plasmacytoid DC (PDC) were detected as CD11c-, CD14-, CD123-high, and BDCA-2+ (3).

To assess the maturation status of the MDC-1, MDC-2, and PDC subsets before and after sunitinib administration, median fluorescence indices of HLA-DR, CD40, and/or CD86 were calculated by dividing the median fluorescence of the test antibody by the median fluorescence of the isotype-matched control antibody (BD Biosciences).

Plasma levels of IL-6, IL-10, and VEGF. After the first centrifugation step of the Vacutainer CPT Cell Preparation Tube and before harvesting the PBMCs, citrate plasma was collected to measure circulating IL-6 and VEGF levels.
IL-10 levels by the use of commercially available ELISA kits, following the manufacturers’ instructions (both from Sanquin). VEGF levels were determined in EDTA plasma samples by ELISA following the manufacturers’ instructions (R&D Systems).

Statistical analysis. The Mann-Whitney U test was used to determine significance of differences between patient and healthy donor data. Patient data of multiple time points or groups were compared using ANOVA. Post hoc analysis of these differences between the time points or response groups was done by the Bonferroni correction for multiple comparisons. Correlations between continuous data sets were analyzed using Spearman correlation coefficient. Kaplan-Meier plots, and log-rank analysis were applied to determine the significance of differences in PFS. Values of $P < 0.05$ (two tailed) were considered statistically significant.

Results

Patients and healthy donors. Twenty-six advanced RCC patients treated with sunitinib were enrolled in the DC monitoring study. Patient characteristics were as follows: in 20 patients (77%), tumors were of clear-cell histology; mean age was 62 years (range, 41-82); 6 patients (23%) were female and 14 patients (54%) had received prior systemic cytokine therapy (IFN-α). Two patients were pretreated with an experimental VEGFR tyrosine kinase inhibitor. Seventeen patients (65%) had undergone an nephrectomy for their disease. Two patients had a good prognosis, whereas 16 patients had an intermediate and 8 patients had a poor prognosis according

Fig. 2. A, differential leukocyte analysis in RCC patients during the first cycle of sunitinib treatment. Gray bars, reference ranges for the indicated leukocyte populations. B, MDC-1 and MDC-2 frequencies as a percentage of myeloid leukocytes (i.e., granulocytes and monocytes) in healthy donors and RCC patients before, and 4 and 6 wk after start of sunitinib. Week 6 represents the time point after the 2-wk period of rest. Individual data and the mean values are shown.
to the Memorial Sloan Kettering Cancer Center prognostic factors (30). There was a minimum period of 4 weeks between previous treatment and the start of sunitinib administration.

During the period of DC monitoring in the first cycle, 33% of the patients experienced any grade of leukopenia, including 1 patient with grade 3, and 13% of the patients experienced any grade of neutropenia, including 1 patient with grade 3. Due to treatment-related side effects, sunitinib treatment was stopped in one patient before tumor evaluation. This patient was not included in the efficacy analysis. As best response, tumor regression was observed in 8 patients (32%) and 11 patients (44%) had stable disease. Six patients (24%) had progression. Median PFS was 5.8 months.

The control group consisted of 10 age- and gender-matched healthy donors (3 women, 7 men; mean age, 60 years; range, 55-68; P = 0.6 compared with RCC patients).

**Sunitinib-induced changes in immature myeloid cell and MSC frequencies.** Although not significant, ImC frequencies as percentage of PBMCs were slightly lower in RCC patients than in healthy donors (0.50% versus 0.72%, respectively; P = 0.2; Fig. 1A). Upon sunitinib treatment, ImC frequencies rose but went down again to baseline levels after the 2 weeks of rest (Fig. 1A). Opposite trends were observed for MSCs, which were defined as positive for CD14 with low or negative HLA-DR expression. As recently reported for a heterogeneous group of advanced cancer patients (3, 14), we also observed an increased frequency of MSCs as percentage of PBMCs in the RCC patients (patients 0.92% versus controls 0.42%; P = 0.09; Fig. 1A). In contrast to ImCs, MSC frequencies decreased on sunitinib treatment but went back up to baseline levels after the 2-week off period.

**Sunitinib-induced changes in classic MDC and PDC frequencies.** Mean frequencies in the mononuclear cell population of all three PBDC subsets (Table 1) were significantly lower at baseline in RCC patients compared with frequencies in healthy donors (Fig. 1B). Absolute numbers of MDC-1, MDC-2, and PDC per milliliter of blood were also significantly lower at baseline in RCC patients compared with healthy donors (data not shown).

During sunitinib treatment, MDC-1 and MDC-2 frequencies decreased, but both MDC-1 and MDC-2 rates went up again after the 2-week off period (Bonferroni-correction: MDC-1, P = 0.008; MDC-2, P < 0.001). Of note, average MDC-1 frequencies even reached levels comparable with those observed in healthy donors (Fig. 1B). PDC frequencies showed similar trends, but changes were not significantly different (Fig. 1B).

To assess the maturation status of the MDC-1, MDC-2, and PDC subsets before and after the first cycle of sunitinib treatment, expression levels of HLA-DR, CD40, and/or CD86 were determined. CD86 and HLA-DR expression levels on the MDC-1 subset in RCC patients were significantly lower than in healthy donors but did not change upon sunitinib treatment (Fig. 1C). Comparing RCC patients with healthy donors, no significant differences were found for HLA-DR, CD86, and/or CD40 expression on both MDC-2 and PDCs, nor did sunitinib change these expression levels (Fig. 1C; data not shown).

**Abnormal distribution of myeloid lineage subsets normalizes upon sunitinib treatment.** RCC patients often have a disturbed blood profile of myeloid leukocytes, possibly associated with a tumor-induced paraneoplastic syndrome (22). Our patient group showed mean baseline levels of neutrophils and monocytes as high as the upper limit of normal values, with levels exceeding the reference range in a considerable number of patients (Fig. 2A). Phase III studies of sunitinib have clearly shown a drug-induced decrease in neutrophil counts (17, 31). This finding was confirmed by our study: the high neutrophil and monocyte counts normalized upon sunitinib treatment and remained low after the 2-week off period (Fig. 2A). To assess the overall myeloid normalization upon sunitinib treatment, we calculated the PBDC frequencies as percentage of myeloid leukocytes. Baseline frequencies of MDC-1, MDC-2, or PDC as percentage of myeloid leukocytes were significantly decreased in RCC patients compared with those in healthy donors (Fig. 2B). Upon sunitinib treatment, including the 2 weeks of rest, the frequencies of MDC-1 and MDC-2 as percentage of myeloid leukocytes increased significantly (Fig. 2B), whereas PDC frequencies did not (data not shown). Importantly, for the MDC-1 subset, relative frequencies measured at week 6 did not significantly differ from those in healthy donors (Fig. 2B).

**Abnormal myeloid distribution is related to IL-6.** IL-6 levels decreased upon sunitinib and increased again after the 2 weeks of rest [mean values (SD) in pg/mL at baseline, 60.1 (93.9); week 4, 27.1 (28.1); and week 6, 45.2 (64.0)]; these changes were not significant by ANOVA. In keeping with previous reports (27, 32), we observed a trend, albeit not significant, toward increased VEGF levels after sunitinib administration, with a subsequent decrease in the 2-week off period [mean values (SD) in pg/mL at baseline, 156.5 (156.6); week 4, 304.8 (382.1); and week 6, 117.6 (87.0)]. Of note, plasma VEGF
levels at baseline were abnormally high compared with reported data (32). IL-10 levels showed small, nonsignificant increases throughout the whole first cycle of sunitinib [mean values (SD) in pg/mL at baseline, 69.2 (77.1); week 4, 98.7 (83.7); and week 6, 118.9 (54.8)].

As mentioned, RCC-related abnormal peripheral distribution of myeloid subsets may be caused by tumor-derived IL-6 (22). Indeed, a significant negative correlation was observed between baseline IL-6 levels and baseline MDC-1 frequencies (Spearman’s rho, -0.58; P = 0.005; Fig. 3) as well as a significant positive correlation between IL-6 levels and neutrophil counts at baseline (Spearman’s rho, -0.63; P = 0.004; Fig. 3). In addition, significant correlations were found between baseline IL-6 levels and baseline MDC-2 or monocytes (Spearman’s rho, -0.49; P = 0.03; rho, 0.60; P = 0.007, respectively; data not shown). In contrast, we did not observe a correlation between baseline IL-6 levels and baseline lymphocyte counts. No correlations were found between levels of VEGF or IL-10, and MDC-1 frequencies or frequencies of any other myeloid subsets (data not shown).

Fig. 4. A, baseline and posttreatment (week 6) counts of neutrophils and monocytes in sunitinib-treated RCC patients in relation to tumor response. B, baseline MDC-1 and MDC-2 frequencies as percentage of mononuclear cells in relation to tumor response. C, baseline and posttreatment (week 6) counts of MDC-1 and MDC-2 as percentage of myeloid leukocytes in sunitinib-treated RCC patients in relation to tumor response. Individual data and the mean values are shown.
Myeloid leukocyte profiles in relation to tumor response upon sunitinib: predictive value of MDC-1 frequencies. The relationship between myeloid lineage subset distribution and tumor response was determined in those patients for whom both variables were available. High baseline counts of neutrophils and monocytes were associated with a lack of tumor response to sunitinib (Fig. 4B), whereas baseline lymphocyte counts were not associated with response (data not shown). In contrast, baseline MDC-1 frequencies as percentage of PBMCs were significantly higher in patients experiencing a regression compared with MDC-1 frequencies in patients with stable disease \((P = 0.02)\) or progression \((P = 0.004)\) as best response (Fig. 4B). This association could not be established for MDC-2 frequencies and tumor response (Fig. 4B).

After treatment, MDC-1 and MDC-2 frequencies as percentage of myeloid leukocytes significantly increased to high levels, even exceeding those observed in healthy donors, specifically in the patients experiencing tumor regression (Fig. 4C). Unlike the “classic” MDC subsets, neither baseline PDC frequencies, nor subsequent therapy-induced changes in PDC frequencies were associated with tumor response (data not shown).

We observed a significant correlation between the decrease in tumor size and high MDC-1 frequencies as percentage of PBMCs both at baseline (Spearman’s rho, \(-0.56; P = 0.007\)) and posttreatment (Spearman’s rho, \(-0.62; P = 0.006\); Fig. 5A). Of note, no such correlation was observed for the MDC-2 subset (Fig. 5B). This correlation between MDC-1 frequencies and therapy-induced changes in tumor size also translated into prolonged PFS: on univariate analysis, a high (i.e., above median) baseline MDC-1 frequency as a percentage of PBMCs was prognostic for a better PFS (log-rank, \(P = 0.04\); Fig. 5C).
In contrast, high baseline frequencies of MDC-2 were not associated with prolonged PFS (Fig. 5D).

**Discussion**

In the present study, we evaluated different PBDC subsets and their precursor populations in advanced RCC patients treated with sunitinib. As compared with healthy donors, we found abnormally high levels of neutrophils and monocytes, and low levels of PBDC frequencies reflecting more mature DC precursors. Our finding of low frequencies of both ImCs, which contrasts with previous reports (1, 4), and PBDCs is indicative of a very early block in MDC differentiation in patients with advanced RCC that seems to be accompanied by increased levels of MSCs. Monocytes, macrophages, and neutrophils have been implicated in T-cell suppression through their production of effector molecules such as arginase and hydrogen peroxide (33–36), whereas decreased PBDC frequencies may further aggravate these immune suppressive effects by a generalized reduction in antigen presentation and T-cell stimulatory capacity. Altogether, this abnormal distribution of myeloid lineage subsets observed in advanced RCC patients is consistent with an immunosuppressed state and may contribute to tumor progression.

After 4 weeks of treatment of the RCC patients, sunitinib induced significant decreases in peripheral blood frequencies of all studied myeloid populations, except for the ImCs, which actually increased in frequency. The latter observation might reflect a temporary relief of a block in early MDC differentiation. However, because total leukocyte counts decreased upon sunitinib, absolute numbers of ImCs did not significantly change in the first treatment cycle (data not shown). We also observed a decrease in MDC frequencies as a percentage of mononuclear cells after 4 weeks of sunitinib. After the subsequent 2-week period of rest, neutrophils and monocytes remained low and were within the range of normal levels as observed in healthy donors, whereas MDC frequencies significantly increased again. This increase was particularly apparent for MDC-1 frequencies, which on average reached levels in healthy donors. The combined lowering of abnormally high levels of immunosuppressive myeloid leukocytes and a relative increase of immunostimulatory MDC-1 frequencies, the latter specifically in patients with tumor regression, suggests that the observed myeloid lineage redistribution in the sunitinib-treated RCC patients results in an overall improved immune status. Whether the myeloid redistribution might actually contribute to, rather than merely result from, the sunitinib-induced antitumor response, remains unresolved. Also, our results are limited to the first cycle of sunitinib treatment. It would be very interesting to investigate whether long-term treatment with sunitinib induces an even more profound and sustained myeloid lineage redistribution in advanced RCC patients.

 Whereas high MDC-1 frequencies were associated with decreases in tumor size and prolonged PFS, this was not the case for the MDC-2 subset, suggesting that MDC-1 plays a more important role in the immunocompetence of RCC patients. In keeping with this, we only found a decrease in phenotypic activation status, as determined by HLA-DR and CD86 expression levels, in the MDC-1 subset. One cycle of sunitinib treatment could not correct for this: HLA-DR and CD86 expression levels remained at the same reduced level as baseline. It remains to be investigated whether sunitinib has actually improved antigen-presenting functions of MDCs on a “per cell basis,” e.g., through ex vivo T-cell stimulations. Due to limited amounts of blood available to us, we were unable to do so. Nevertheless, baseline MDC-1 frequencies were positively associated with prolonged PFS, suggesting that increased MDC-1 frequencies with reduced activation status may still contribute to the immunocompetence of RCC patients. Possibly, upon recruitment to peripheral tissues, immature MDC-1 precursors from the blood can rapidly mature to competent DC with up-regulated levels of costimulatory and MHC molecules.

Because sunitinib is a promiscuous agent inhibiting multiple receptor tyrosine kinases, it is hard to establish which receptor or pathway was targeted to achieve the effects on myeloid differentiation as observed in our study. The sunitinib-induced generalized decrease in frequencies of myeloid subsets are likely to result from its fms-like tyrosine kinase-3 or KIT inhibitory activity (37, 38) because both pathways have shown their importance in early stages of myeloid cell differentiation (18). The mechanism underlying the observed increase in MDC-1 frequencies is harder to unravel. Although interference with VEGFR signaling might be an obvious explanation, we could not establish a correlation between VEGF levels and baseline MDC-1 frequencies in our study population. We did, however, find a negative correlation between baseline IL-6 levels and baseline MDC-1 and MDC-2 frequencies. The relevance of this association has previously been confirmed in a preclinical RCC study, in which tumor-derived IL-6 was found to cause defective DC differentiation (39). Sunitinib may alter the responsiveness of MDCs, or possibly of an earlier DC precursor, to IL-6, as MDC frequencies increase during the 2-week rest period despite a simultaneous increase in IL-6 levels. Regarding this possibly altered IL-6 responsiveness, it is of particular interest that sunitinib can inhibit phosphorylation of signaling transduction and activator of transcription 3, a signaling molecule downstream of the IL-6 receptor (40, 41). Modulating signal transducers and activators of transcription 3 activation in DCs might result in an decreased responsiveness to the inhibitory activity of IL-6 (42), which subsequently might lead to increased MDC frequencies. We did a pilot study to determine the signaling transduction and activator of transcription inhibitory effects of sunitinib in PBMCs of five RCC patients treated with this agent. We were able to detect signaling transduction and activator of transcription expression in PBMCs by Western blot analysis, but a modulatory effect of sunitinib was not conclusively established and will require further investigation in larger numbers of patients (Supplementary Fig. S1).

Until recently, IFN-α immunotherapy was the standard of care in locally advanced or metastatic RCC. The efficacy of sunitinib has changed the first- and second-line treatment for this disease (15–17). Patients with RCC, however, eventually suffer from tumor progression after initial tumor regression upon VEGFR-interfering therapy. Hence, oncologists have a growing interest in regimens combining immunotherapy with agents interfering with VEGFR signaling. Our observation that sunitinib treatment, at least in part, normalizes disturbed myeloid differentiation pathways, resulting in a potentially more favorable immunocompetent state, certainly supports this.
References


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