β₂-microglobulin serum levels, and high C-reactive protein values. We did not observe any correlation between p16\(^{ink4a}\) methylation and the initial characteristics of the patients. However we observed almost the same differences in OS and PFS as Mateos et al. did. Ng et al. reported similar incidences of p16\(^{ink4a}\) gene methylation in pre-treated and post-treated MM patients. These findings suggest that in spite of possible variations between techniques used, heterogeneity of patients, and other unknown factors, p16\(^{ink4a}\) methylation analysis in MM might provide interesting prognostic information and warrants future prospective studies.

The absence of prognostic impact of p15\(^{ink4b}\) gene methylation is in marked contrast with the prognostic value of p16\(^{ink4a}\) methylation. We previously reported frequent methylation of p15\(^{ink4b}\) and p16\(^{ink4a}\) genes in CD138-purified plasma cells from patients with monoclonal gammapathy of undetermined significance, suggesting that methylation of p15\(^{ink4b}\) and p16\(^{ink4a}\) might be an early event in the course of MM. Combined with our current findings, these data suggest that both p15\(^{ink4b}\) and p16\(^{ink4a}\) methylation might play a role in the initial transformation of plasma cells. However, p15\(^{ink4b}\) methylation might exert a lesser influence on subsequent tumor progression.

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References

Non-myeloablative stem cell transplantation with low-dose total body irradiation and fludarabine for metastatic renal cell carcinoma

We evaluated the feasibility of non-myeloablative stem cell transplantation for metastatic renal cell carcinoma after a non-myeloablative conditioning regimen combining low-dose TBI and fludarabine. Seven consecutive patients were included. Initial engraftment occurred in all patients and 6/6 evaluable patients achieved sustained donor chimerism. One patient experienced a partial response but the other 6 progressed.

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Metastatic renal cell carcinoma (RCC) is largely insensitive to chemotherapy. In 2000, Chmiel et al. recently proposed an original approach to NMSCT with a conditioning regimen based on 2 Gy TBI + fludarabine, followed by post-transplant immunosuppression with cyclosporine A (CyA) and mycophenolate mofetil (MMF) that permitted the transplant to be performed in an ambulatory care setting. In the present study, we report our experience with 7 patients with RCC. Seven consecutive patients with metastatic RCC were included (Table 1). Written informed consent was obtained from patients and donors and our institution’s Ethical Committee approved the protocol. Four patients had HLA-identical siblings and three had alternative donors. Conditioning consisted in 90 mg/m² fludarabine combined with 2 Gy TBI. The whole post-transplant procedure was carried out as outpatient except in the haemodialyzed patient. Post-transplant immunosuppression consisted in CyA and MMF. Disease responses were defined using the criteria of Chlids et al. Stem cell mobilization and collection were carried out as previously reported. The protocol involved a prospective comparison of graft manipulation, so that patients #1–3 received unmobilized PBSC, patients #4–6 CD8-depleted PBSC and patient #7 CD34-selected PBSC. Three patients without GVHD received additional DLI (per protocol) on days 40 and 80. Per protocol, DLI were unmanipulated in patient 2 and CD8-depleted in patients #5 and 7. Chimerism was assessed as previously reported.

None of the patients developed grade ≥2 regimen-related toxicity. The neutrophil nadir occurred on day 7 and was 0.97×10^9/L (0.12–1.67). Two patients did not require hospitalization within the first 30 days following NMSCT, and the other five were hospitalized for a median of 9 (6–22) days. Total white blood cell (WBC) and CD3+ cell chimerisms were 91% (90–96) and 67% (20–89) on day 7 and 95 (95–96) and 83 (32–96) on day 100, respectively (Figures 1A and 1B).

We observed only 1 partial response. This response occurred in patient #1 who had extensive lung metastases. The disease remained stable the first 150 days after transplantation (Figure 1C) but the tumor mass was markedly (> 50%) reduced on day 240. This patient experienced both acute and chronic GVHD. Response persisted until day 389 when a chest CT-scan showed elimination or major reduction of 80% of the metastases with stabilization of the others, with the exception of two lesions that progressed (Figure 1D). Unfortunately the patient subsequently relapsed in the liver and died of disease progression. All other patients progressed (Table 1). We show here that engraftment can be achieved in RCC patients with this low-intensity...
Letters to the Editor

Figure 1. Evolution of myeloid (A) and T-cell (B) chimerism in the 5 RCC patients who survived more than 50 days after the transplant. (C-D) Chest CT scan in patient 1. The disease remained stable the first 150 days after transplantation (C) but the tumor mass was markedly (>50%) reduced on day 240. Response persisted until day 389 (D) with elimination or major reduction of 80% of the metastases (large arrow) and stabilization of the others, except two lesions that progressed (one is indicated by the small arrow).

Table 1. Patients, donors and clinical evolution.

<table>
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<th>Patients</th>
<th>#1</th>
<th>#2</th>
<th>#3</th>
<th>#4</th>
<th>#5</th>
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<th>#7</th>
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<td>2</td>
<td>5</td>
<td>4</td>
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<td>2×2</td>
<td>15×6.5</td>
<td>5×5</td>
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<td>Septic</td>
<td>Pain (progression)</td>
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<td>Death(151)</td>
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<td>Death(22)</td>
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</tbody>
</table>

M: male; F: female; HLAid: HLA identical; PR: partial response; PD: progressive disease; 1MM: one HLA mismatch; N/A: not applicable; 
*after DLI: interferon-α therapy and CyA withdrawal.
regimen. Furthermore, we demonstrate for the first time that alternative donors can be used successfully for this purpose. Moreover, our results evidence that nearly full donor chimerism can be achieved in the majority of RCC patients treated with this approach, even in recipients of CD8-depleted or CD34-selected PBSC. Patients included in our study experienced less toxicity than patients reported by Childs et al.: the neutrophil count fell below 0.5×10⁹/L in 1/7 patients compared with 19/19 patients in the study of Child et al. and none of our patients experienced grade >2. Bearman toxicities nor died of transplant-related complications.

Although the primary aim of this pilot study was not to assess the occurrence of a graft-versus-tumor effect but to evaluate the feasibility of this low-intensity technique in the RCC setting, we observed a response in 1 of 7 patients. Patient 1 achieved a partial response 8 months after the transplant in the context of extensive chronic GVHD, demonstrating that immune responses can be obtained after this low-intensity NMSCT approach. However, as illustrated in patients #4-7, this approach should not be offered to patients with very advanced disease at the time of transplant. The time necessary to identify a donor and organize the transplant, as well as the delay between transplantation and any significant tumor response, should restrict the applicability of this approach to patients with less advanced disease.

In conclusion, our study showed the feasibility and low toxicity of NMSCT with 2 Gy TBI plus fludarabine for patients with metastatic RCC. However, this investigational approach should be carried out only in Centers with proven experience in this field and within approved protocols.

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Editorial note. The reader may be interested in articles on alloablative, renal cell carcinoma.

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