at the CALCA gene promoter (Figure 1). CALCA was chosen as marker because of reported hypermethylation in childhood MDS. Our patient initially showed 55.4% CALCA methylation in the peripheral blood, which decreased to 4.5% before the eighth cycle of AC. Importantly, reduction in methylation was not only due to clearance of malignant cells, but was evident in the clone itself. Before the third cycle, 58% of cells still carried methylation.\footnote{Before the third cycle, 58\% of cells still carried methylation.} The favorable response fits well with previous studies\cite{rueter-2010, roder-2010} but has additional remarkable aspects. Thrombocytopenia and HbF at diagnosis indicated that this was a rather aggressive case of JMML. Using conventional cytostatic therapy, remissions are rare in these cases\cite{rajkumar-2010} and disappearance of the monosomy 7 clone in JMML without HSCT has never been reported before. In summary, our results suggest that AC therapy may be a viable option for JMML/monosomy 7 patients, either as a pretransplant window or in the absence of a suitable HSCT donor.

Here we report the first patient with JMML and monosomy 7 treated with AC. The favorable response fits well with previous studies\cite{rueter-2010, roder-2010} but has additional remarkable aspects. Thrombocytopenia and HbF at diagnosis indicated that this was a rather aggressive case of JMML.\footnote{Before the third cycle, 58\% of cells still carried methylation.} Using conventional cytostatic therapy, remissions are rare in these cases\cite{rajkumar-2010} and disappearance of the monosomy 7 clone in JMML without HSCT has never been reported before. In summary, our results suggest that AC therapy may be a viable option for JMML/monosomy 7 patients, either as a pretransplant window or in the absence of a suitable HSCT donor.

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References


To the editor:

Etanercept for treatment of idiopathic pneumonia syndrome after allogeneic hematopoietic stem cell transplantation

We read with interest the paper by Yanik and colleagues describing the impact of using soluble tumor necrosis factor (TNF)-α binding protein, etanercept (Enbrel; Amgen, Thousand Oaks, CA) on the treatment of idiopathic pneumonia syndrome (IPS) following allogeneic hematopoietic stem cell transplantation (HSCT).\footnote{We read with interest the paper by Yanik and colleagues describing the impact of using soluble tumor necrosis factor (TNF)-α binding protein, etanercept (Enbrel; Amgen, Thousand Oaks, CA) on the treatment of idiopathic pneumonia syndrome (IPS) following allogeneic hematopoietic stem cell transplantation (HSCT).} The authors describe their experience with 15 patients who developed IPS at a median time of 14 days after HSCT. The overall survival at days 28 and 56 from the first etanercept dose is reported to be 73% and 60%, respectively. One of the main conclusions of the paper is that the combination of corticosteroids and etanercept improves survival. We believe that the data provided support improvement in early survival but did not contribute to improving long-term survival.

Using the data provided in Table 1 of the article by Yanik et al.,\footnote{We used the Kaplan-Meier method to estimate the overall survival at 100 days and at 1 year after diagnosis of IPS for the patients described. The confidence intervals (CIs) are based on the log hazard. The estimated survival at 100 days and at 1 year is 47% (95\% CI: 21, 69) and 20\% (95\% CI: 5, 42), respectively. Twelve of the 13 deaths reported were related transplantation-related causes and 1 was related to relapsed disease. The same group reported on 3 pediatric patients treated with etanercept for IPS, and all 3 patients responded to the initial therapy but died before 120 days after transplantation (2 related to organ dysfunction and 1 related to relapsed disease).} we used the Kaplan-Meier method to estimate the overall survival at 100 days and at 1 year after diagnosis of IPS for the patients described. The confidence intervals (CIs) are based on the log hazard. The estimated survival at 100 days and at 1 year is 47\% (95\% CI: 21, 69) and 20\% (95\% CI: 5, 42), respectively. Twelve of the 13 deaths reported were related transplantation-related causes and 1 was related to relapsed disease. The same group reported on 3 pediatric patients treated with etanercept for IPS, and all 3 patients responded to the initial therapy but died before 120 days after transplantation (2 related to organ dysfunction and 1 related to relapsed disease).\footnote{We used the Kaplan-Meier method to estimate the overall survival at 100 days and at 1 year after diagnosis of IPS for the patients described. The confidence intervals (CIs) are based on the log hazard. The estimated survival at 100 days and at 1 year is 47\% (95\% CI: 21, 69) and 20\% (95\% CI: 5, 42), respectively. Twelve of the 13 deaths reported were related transplantation-related causes and 1 was related to relapsed disease. The same group reported on 3 pediatric patients treated with etanercept for IPS, and all 3 patients responded to the initial therapy but died before 120 days after transplantation (2 related to organ dysfunction and 1 related to relapsed disease).}

We have reported the outcome with 11 pediatric patients who developed IPS at a median of 17 days after allogeneic HSCT.\footnote{We have reported the outcome with 11 pediatric patients who developed IPS at a median of 17 days after allogeneic HSCT.} Five of the 11 patients required assisted ventilation. All patients were treated with corticosteroid, and those who did not respond to corticosteroid therapy were treated with etanercept (n = 3) or infliximab (Remicade; Centocor, Malvern, PA; n = 3). Nine of the 11 patients (81\%) had resolution of respiratory symptoms and were weaned off oxygen. The overall survival at 100 days and at 1 year after the diagnosis of IPS was 73\% (95\% CI: 37, 90) and 32\% (95\% CI: 8, 60), respectively. A large study by the Seattle group reported on the outcome of 81 patients with IPS among 1100 patients who underwent myeloablative or nonmyeloablative HSCT.\footnote{A large study by the Seattle group reported on the outcome of 81 patients with IPS among 1100 patients who underwent myeloablative or nonmyeloablative HSCT.} Despite aggressive supportive care, the 100-day and 1-year survival after diagnosis of IPS was 23\% and 17\%, respectively. None of the patients were treated with anti-TNF therapy.

Although treatment with corticosteroids and etanercept improved the short-term survival (day 56) for patients with IPS, the overall survival at 1 year was not impacted by this therapy compared with patients who only received supportive care. The development of lung injury after allogeneic HSCT represents a poor prognostic indicator regardless of the response to the initial therapy. Future strategies should not only address the early mortality associated with IPS but also the long-term high rate of transplantation-related mortality in this subset of patients.

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Response:

Etanercept for idiopathic pneumonia syndrome

We appreciate Dr Frangoul’s comments regarding long-term survival of the patients reported in our article.\(^1\) Idiopathic pneumonia syndrome (IPS) remains a leading cause of treatment-related mortality, with one-month mortality rates approaching 80%. The goal of our study was to determine whether tumor necrosis factor (TNF) inhibition with 4 weeks of etanercept therapy could overcome the short-term risk of death. In our study, short-term mortality was reduced to 27%. Responders to etanercept therapy exhibited a median survival of 217 days (range, 46-1424), compared with 17 days (range, 4-55) for nonresponders. Because our trial was not designed to determine whether etanercept treatment improves long-term survival, we can only speculate on why no obvious improvement in long term survival was observed. Graft-versus-host disease (GVHD), another process in which TNF plays a critical role, was a major contributor to subsequent mortality in our study population. We observed transient responses in GVHD in several patients receiving study therapy. It is possible that a longer course of etanercept might have favorably impacted long-term survival, as shown in a recent study of etanercept for the treatment of acute GVHD.\(^1\)

As discussed in the body of the text, we believe the current pilot study represents an example of translational research wherein laboratory insights using established animal models of human disease were directly transformed into a novel treatment strategy for a frequently fatal clinical complication. Our data demonstrate that the addition of etanercept to standard dose corticosteroids and supportive care measures is associated with encouraging response rates, reductions in systemic and pulmonary inflammation, and an acceptable toxicity profile. Based upon these favorable results, a phase 2 pediatric trial through the Children’s Oncology Group (COG) and the Pediatric Blood and Marrow Transplant Consortium (PBMT), and a phase 3, randomized, placebo controlled, trial through the BMT Clinical Trials Network (BMT CTN) are currently in progress. In each, the impact of TNF inhibition on both short- and long-term survival after IPS will be examined.

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Reference

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