Pentostatin (2'-deoxycoformycin) for the treatment of hepatosplenic γδ T-cell lymphomas

We report the results of treatment with single agent 2'-deoxycoformycin (Pentostatin) in two patients with Hepatosplenic γδ T-cell lymphoma (HSγδTCL), a rare lymphoma subtype with a highly unfavorable prognosis. Present and previous data reviewed here demonstrates the striking cytotoxic activity of Pentostatin against γδ+ tumor T-cells. Further studies are warranted to define the optimal strategy to fully exploit therapeutic potential of this drug in patients with HSγδTCL.

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Hepatosplenic γδ T-cell lymphoma (HSγδTCL) was first identified by Farcet and Gaulard in 1990 as a distinct lymphoma entity with unique clinicopathologic features and a poor clinical outcome.1 Subsequent case series confirmed the highly unfavorable prognosis of this lymphoma emphasizing how current therapeutic strategies are mostly ineffective.[1-4] Following an initial response to CHOP-like regimes most patients ultimately succumb to the disease despite consolidative or salvage high-dose therapy.[2-4] New treatment strategies are therefore needed. We were the first to document the potent and selective cytotoxic effect of 2'-deoxycoformycin (Pentostatin) in a patient with HSγδTCL,[5] and treatment of additional two patients by other investigators confirmed the impressive activity of this drug in HSγδTCL.[6,7] Following our report,5 we treated two more patients with Pentostatin (5 mg/m^2, day 1-3, every three weeks).

The first was a 38-year old female, who, following splenectomy, refused chemotherapy and received daily cyclophosphamide (50 mg) and prednisone for one year as a part of a unconventional cancer treatment ('Di Bella Multitherapy'). She was in stage IVA at diagnosis with bone marrow involvement (50% of CD3$^+$ tumor T-cells with intrasinusoidal pattern) and the histologic examination of the spleen displayed infiltration of red pulp cords and sinuses by atypical small and medium sized tumor cells (CD3$^+$, CD4-, CD8-) which also tended to form intravascular clusters. At progression, she presented in very poor clinical conditions with B symptoms, massive hepatomegaly (maximal craniocaudal diameter –MCD- at ultrasonography, 32 cm), massive bone marrow involvement (80% of γδ+ tumor cells), overt leukemic phase (WBC, 22.5×10^9/L) with 84% of circulating γδ$^+$ tumor T-cells (CD3$^+$, TCRαβ$^-$, CD5$^-$, CD4$^-$, CD8$^-$, CD56$^+$), thrombocytopenia (13.0×10^9/L) and slight elevation of aspartate (AST; 71/35 U/L) and alanine (ALT; 72/40 U/L) aminotransferases, lactate dehydrogenase (LDH; 257/190 U/L), D-bilirubin (1.62 mg/dL) and γ glutamil transferase (gGT; 318/45 U/L) serum levels. Four days after the first Pentostatin infusion, the liver size was reduced by 50% (MCD, 16 cm), circulating γδ+ tumor cells were 1.98×10^9/L and platelets count rose to 32.0×10^9/L. Unfortunately, at day +5 the patient developed a fatal respiratory distress syndrome.

The second patient was a 39-year old male treated 7 years before for Hodgkin's disease. He presented with steroid-unresponsive hyperpyrexia, severe jaundice (D-bilirubin 24.48 mg/dL), hepatomegaly (MCD, 23.2 cm) and splenomegaly (MCD, 19.4 cm). Positron emission tomography (PET) with fluoro-deoxyglucose (FDG) evidenced hyper intense uptake by bone marrow and liver plus several FDG-avid spleen nodules. Bone marrow was infiltrated by γδ$^+$ T-cells (40%) with a typical intrasinusoidal pattern. Anemia (Hb 7.3 g/dL), neutropenia (0.5×10^9/L), lymphopenia (0.2×10^9/L), elevation of serum transaminases (AST 682 U/L; ALT 311 U/L), LDH (1256 U/L), ÁGT (731 U/L) and alkaline phosphatase (AP, 1755 U/L), were also present. Due to the severe disease-related jaundice, hampering the upfront use of anthracyclines and vincristine, we treated the patient with high-dose Methylprednisone (30 mg/kg i.v. daily) followed by 'fractionated' cyclophosphamide (400 mg/m^2 i.v. daily, for 5 days). We speculated that an initial tumor shrinkage would have led to a reduction in bilirubin levels allowing a later use of other drugs. Unfortunately, such approach was ineffective and d-bilirubin levels remained at 22.64 mg/dL at the end of treatment. In contrast, five days after starting Pentostatin, the patient became apyretic and by two weeks D-bilirubin levels dropped to normal values. After four weeks, spleen and liver sizes were reduced by >50% with disappearance of all FDG-avid nodules. Transaminases (AST 98 U/L; ALT 139 U/L), LDH (594 U/L) and AP (334 U/L) were significantly reduced and the hemogram improved (Hb 8.4 g/dL, neutrophils 3.0 x 109/L, lymphocytes 0.5 x 10^9/L). A second course of Pentostatin was administered with further reduction of spleen and liver sizes to normal limits but two weeks afterwards the patient, developed cough, chest pain, dyspnea and meropenem/teicoplanin-resistant intermittent fever (38.5-39.5 C°). Blood samples for cytomegalovirus (CMV) detection were obtained and the patient was started on intravenous Gancyclovir. High resolution CT scans of the thorax displayed bilateral dense regional consolidations and acinar/macronodular cavitary lesions suggestive of fungal infection. Blood CMV PCR testing was negative, while cytologic evaluation of bronchoalveolar lavage excluded mycobacterial and Pneumocystis infections being instead positive for Aspergillus. Death from respiratory failure occurred 8 days later, i.e. three weeks after the second course of Pentostatin, despite Amphotericin B therapy.

It is not clear whether the development of pulmonary Aspergillosis in this patient could be related to Pentostatin treatment, since the majority of non-Pneumocystis infections described for patients receiving nucleoside analogs are of bacterial and viral etiology. Fungal infections, however, are increasingly been described as a terminal event in such patients. Our patient had received daily prednisone treatment (25 to 50 mg) for two months before admission at our Center and was on continuous trimetoprim/sulphametoxazole and fluconazole (400 mg daily) prophylaxis from the third week after the first course of Pentostatin. Whether fluconazole prophylaxis might have increased the risk for a non-*Candida spp* fungal infection is a matter of speculation. On the other hand, previous treatment with steroids and cyclophosphamide might have further lowered the threshold for unusual infections in this patient. Since Pentostatin rarely induces severe myelosuppression, it appears reasonable that Pneumocystis Carinii prophylaxis and timely CMV testing should remain the most appropriate measures for patients treated with this drug, especially in those receiving concomitant corticosteroids. Finally, since it has been suggested that neoplastic transformation in HSγδTCL results from a multistep process involving the impairment of the immune system,4 the occurrence of unexpected infections in these patients might also in part reflect the peculiar biology of this disease.

While the activity of Pentostatin in other subtypes of T-cell lymphomas is well established, only 5 patients with

Table 1. Summary of patients with Hepatosplenic γδ T-cell lymphoma treated with Pentostatin (previous and present reports).

	Age/Sex*	*Previous Therapy*	*Sites of involvement**	*Pentostatin schedule*	*Ref.*
#1	34/F	CHVmP/BV, α–-IFN, splenectomy	Liver, bone marrow, peripheral blood, B symptoms	4 mg/m^2 q 7 days x 3 courses then q 14 days x 1 course	5
#2	33/F	PDN, CSA, CHOP, Compound 50607, HiDEX, α–IFN, Fludarabine/Cisplatin/ARA-C, ARA-C, Etanercept	Liver, spleen, pleural effusion, B symptoms	4 mg/m^2 q 14 days, then q 28 days (13 courses)	6
#3	42/M	None	Liver, spleen, bone marrow, B symptoms	4 mg/m^2 q 14 days (10 courses)	7
#4	38/F	Splenectomy, CTX	Liver, bone marrow, peripheral blood, B symptoms	5 mg/m^2, day 1-3, q 21 days	Present report
#5	39/M	MOPP + RT (HD), methyl-PDN, CTX	Liver, spleen, bone marrow, B symptoms	5 mg/m^2, day 1-3, q 21 days	Present report

**At starting of Pentostatin. CHVmP/BV: cyclophosphamide, doxorubicin, teniposide, prednisone, vincristine, bleomycin; IFN: interferon; PDN: prednisone; CSA: cyclosporin A; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; HiDEX: high-dose dexamethasone; CTX: cyclophosphamide; MOPP: mecloretamine, vincristine, procarbazine, prednisone; RT: radiotherapy; HD: Hodgkin's disease.*

Table 2. Summary of therapeutic activity of Pentostatin in patients with Hepatosplenic γδ T-cell lymphoma (previous and present reports).

Patient	*Therapeutic activity*	*Further Therapy and Outcome*
#1	Complete hematologic remission, >50% reduction of hepatomegaly, disappearance of B symptoms	Allogeneic bone marrow transplantation; death due to transplant-related complications
#2	Clinical remission, persistence of slight hepatosplenomegaly	None; alive in clinical remission at 8 months*
#3	Complete clinical and hematologic remission	High dose therapy and autologous PBSC transplantation; alive in complete remission at 12 months post-transplant*
#4	Clearance of circulating γδ tumor T-cells, >50% reduction of hepatomegaly, disappearance of B symptoms	Early death due to acute respiratory distress syndrome
#5	Resolution of hepatosplenomagaly, PET-FDG negativity of bone marrow, liver and spleen, resolution of severe jaundice, disappearance of B symptoms	Death due to invasive fungal infection

**last reported follow-up PBSC: peripheral blood stem cells; PET-FDG: Positron emission tomography with fluoro-deoxyglucose.*

HSgdTCL have been treated to date with this drug (Table 1). Even though available data is limited to draw definitive conclusions, it appears that in HSgdTCL patients Pentostatin treatment is able to induce a rapid clearance of tumor cells from all involved tissues, a prompt reduction of organomegaly along with the disappearance of B symptoms and improvement of the hematologic picture (Table 2).

The optimal strategy and schedule to fully exploit the cytotoxic activity of Pentostatin in HSgdTCL remain to be defined. Weekly and bi-weekly schedules of 4 mg/m2 appear effective and well tolerated,5-7 while more intensive schedules (5 mg/m2 day 1-3, q 21 days)8 in patients with extensive tissue involvement may add risks of an exceedingly rapid tumor cells destruction including respiratory distress syndrome. Since most patients initially respond to CHOP-like regimes, one might exploit the selective action of Pentostatin on gd+ tumor cells5 to eradicate residual disease following tumor debulking by conventional and/or high-dose chemotherapy. Alternatively, the modest myelotoxicity of Pentostatin on weekly schedules,5-7 may prompt its introduction upfront, as a part of a modified MACOP-B-like weekly regime. The recent inclusion of Pentostatin in preparative regimes for non-myeloblative allogeneic stem cell transplantation,9 also suggests that reduced-intensity allotransplantation with Pentostatin-based conditioning may represent a further eradicating strategy for patients with HSgdTCL. Given the rarity of this lymphoma, only prospective multicenter trials will allow the definition of the potential role of Pentostatin in the upfront treatment of HSgdTCL. Our definition of new biological predictors for response to Pentostatin, i.e. CD26 expression, might help designing of such studies.10

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