Characteristics and stage of the underlying diseases could determine the risk of opportunistic infections in patients receiving alemtuzumab

Alemtuzumab is usually associated with opportunistic infections. We have treated 67 patients, 8 non-Hodgkin's lymphoma and 59 chronic lymphocytic leukemia (CLL) with campath. Among CLL patients, 6 used alemtuzumab in first line, alone or with chemotherapy, 41 as consolidation therapy and 11 as salvage therapy, 3 alone and 8 with chemotherapy. In our series opportunistic infections were prevalently found in patients submitted to alemtuzumab salvage therapy (33.3%), with or without chemotherapy; in particular 1 pulmonary nocardiosis, 1 tubercolosis. Also during the first line alemtuzumab therapy one case of lysteriosis and one case of HBV reactivation were found (33.3%). No opportunistic infections were diagnosed to our CLL patients in consolidation therapy, when the underlying hematologic disease was reduced or present only as minimal residual disease. A good response of malignancy, namely CLL, to induction therapy, such as a less aggressive schedule of therapy, determine a lower risk of immunosuppression and therefore a low number of opportunistic infections.

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The recent study published by Bernengo *et al.*[1] regarding low-dose alemtuzumab in 14 patients affected by Sézary syndrome, 11 with relapsed/refractory disease, offers an interesting opportunity to discuss the infectious toxicity of this monoclonal antibody. In their experience, infectious complications were the most frequent non hematological toxicity and were related to dosage of alemtuzumab. Infections were diagnosed in 4 patients (28.65), 3 staphylococcal sepsis, two of them with a spinal epidural abscess and vertebral osteomyelitis respectively, and one cytomegalovirus reactivation with fever. The authors underlined that infectious complications occurred in all the four patients treated with alemtuzumab at dosage up 15 mg (median dose in first cycle 73 mg) and none of patients treated with a maximum dose of 10 mg (median dose in first cycle 13 mg). Another cohort study published last year by Martin *et al.*[2] presented interesting data regarding infectious complications associated to alemtuzumab use in hematologic patients (27 cases) at a single institution , and, in particular in 21 chronic lymphocytic leukemia (CLL) patients. The CLL population was in prevalence submitted to more than 1 line of chemotherapy (100% submitted to fludarabine, 60-70% were previously treated with rituximab and/ or cyclophosphamide probably as second-third line therapy, etc) with a high presence (43%) of opportunistic infections, escluding cytomegalovirus viremia without evidence of organ disease (44% of patients). Among the opportunistic infections of CLL patients there were: invasive pulmonary aspergillosis,[3] adenoviral pneumonia,[1] PML,[1] disseminated histoplasmosis,[1] disseminated cryptococcosis[1] cerebral toxoplasmosis,[1] cytomegalovirus pneumonitis and cholitis.[1] Seven of 10 deaths could be attributed to infection, in 4 cases to opportunistic infections. No difference was found between patients with opportunistic infections or not, regarding cumulative chemotherapy prior to alemtuzumab therapy and time from diagnosis of malignancy to the initiation of alemtuzumab treatment.

Until now we have treated 67 patients, 8 non-Hodgkin's lymphoma and 59 CLL with campath. Herpes virus and *Pneumocystis pneumonia* prophylaxis was usually administered. Among CLL patients, 6 used alemtuzumab in first line, alone or with chemotherapy, 41 as consolidation therapy[3] and 11 as salvage therapy, 3 alone and 8 with chemotherapy. We diagnosed 22/67 cases (32.8%) of CMV reactivation without organ disease. Few opportunistic infections were seen in our population, and in prevalence during first line and salvage therapy. No opportunistic infections were diagnosed to our CLL patients in consolidation therapy, when the underlying hematologic disease was reduced or present only as minimal residual disease. However, in another previous experience,[4] the frequency of alemtuzumab administration (three times per week), performed close to previous chemotherapy, seems to determine more opportunistic infections, probably due to a further increase of immunosuppression. In our series opportunistic infections were prevalently found in patients submitted to alemtuzumab salvage therapy (33.3%), with or without chemotherapy; in particular 1 pulmonary nocardiosis, 1 tubercolosis. Also during the first line alemtuzumab therapy one case of lysteriosis and one case of HBV reactivation were found (33.3%). Opportunistic infections of our patients are summarized in Table 1. Regarding our CLL population, it seems evident that opportunistic infections were diagnosed above all when the hematologic disease was active, at the onset of the malignancy or in presence of resistant/relapsed disease, while they were found less during consolidation therapy, when CLL was in remission or widely reduced . This low number of opportunistic infections when CLL was in remission is similar (4.55) to that published by Peleg *et al.*[5] in organ transplant recipients when they received alemtuzumab at time of transplantation only, as the prophylaxis of acute rejection. The same study reported, instead, a

Table 1. Opportunistic infections (OIs) in patients receiving alemtuzumab during different phases of therapy.

	NHL (8 patients)	*CLL (59 patients)*
OIs in induction	-	2/6 (33.3%) (lysteriosis, HBV)
OIs in consolidation	0/3	0/41
OIs in salvage therapy	2/5 (40%) (TBC, possibile aspergillosis)	3/12 (33.3%) (nocardiosis, IVU, TBC)

higher percentage (21%, $p<0.001$) of opportunistic infections when alentuzumab was administered for the treatment of steroid-refractory acute allograft rejection, without difference between recipients who received alemtuzumab as induction therapy and then as rejection treatment (22%) and those who received it only as rejection therapy initially (21%). As in hematologic patients, several factors may explain these differences in the appearance of opportunistic infections. Probably, the most important is the concomitant exposition to other potent immunosuppressive agents, with a significantly more profound state of immunosuppression. For this reason the characteristics and the stage of underlying disease, and probably also the modality of administration, plays an important role. A good response of malignancy, namely CLL, to induction therapy, such as a less aggressive schedule of consolidation therapy, and, similarly, the absence in the transplant setting of concomitant complications such as rejection, determine a lower risk of immunosuppression and therefore a low number of opportunistic infections. Such data could have implications for deciding prophylaxis strategies.

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