High incidence of infections in HIV-positive patients treated for lymphoproliferative disorders

High Incidence of Infections in HIV-positive Patients Treated for Lymphoproliferative Disorders

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Abstract

Background: Lymphoproliferative disorders are frequently diagnosed in HIV-positive patients and severe infections may occur during antineoplastic treatments: the incidence and impact of such events are not well-characterized.

Objective: To describe the occurrence and mortality of incident infections in HIV-positive individuals treated for lymphoproliferative disorders.

Methods: A retrospective study in HIV-positive adults with lymphoproliferative disorders (2000-2012). Patients were hospitalised to receive antineoplastic chemotherapy; as well as antimicrobial prophylaxis with alternate day co-trimoxazole (800/160 mg).

Results: 103 patients were included: mostly males (81, 78.6%), Caucasians (101, 98.1%), with a median age of 43 years (39-51). Fifty-eight (56.3%) patients had non-Hodgkin's lymphoma (NHL), thirty-two (29.1%) had Hodgkin's lymphoma (HL) and ten patients (9.7%) had Burkitt's lymphoma (BL). Five year survival was 63.1%: the best survival rates were reported in HL (78.1%), followed by NHL (58.6%) and BL (50%). Forty-four patients (42.7%) developed 82 infections during follow up: identified causative agents were bacteria (35, 42.7%), viruses (28, 34.1%), mycobacteria (7, 8.5%), protozoa (7, 8.5%) and fungi (5, 6.1%). Cytomegalovirus infections (n=17, including 5 end-organ diseases) emerged 53 days after the diagnosis: multivariate analysis showed CD4+ cell count <100/uL as the only independently associated factor ($p<0.001$, aOR=23.5). Two factors were associated with mortality risk: a IPI/IPS-score of >2 ($p=0.004$, aOR=6.55) and the presence of CMV disease ($p=0.032$, aOR=2.73)..

Conclusions: HIV positive patients receiving treatment for lymphoproliferative disorders suffer from a high incidence of infections and associated mortality risk. Tailored secondary prophylaxis be beneficial and should be considered in this setting.

Key words: HIV; lymphoma; survival; infection; cytomegalovirus.

Introduction

HIV-positive patients have an increased risk of lymphoproliferative disorders compared to the non-infected population. Standardized incidence rates for NHL are reported to be 103 (88.8-119) in the pre Highly Active Antiretroviral Treatment (HAART) era (1985-1996), 26.7 (19.9-35.1) in the early HAART era (1997-2001) and 16.2 (11.1- 22.9) in the late HAART era (2002-2006). [1] Conversely Hodgkin's lymphoma standardized incidence rates seemed to increase in the late HAART era (from 9.2 to 28.1), accounting for the second most common non-AIDS defining cancer. [1,2] Before the introduction of HAART outcomes in HIV positive patients with lymphomas were very poor, mainly due to the failure of chemotherapy regimens and the development of opportunistic and non-opportunistic infections (with sepsis being frequently reported). [3]

HAART has a great impact on the progression of lymphomas: it has been associated with increased treatment response rates and reduced incidence of opportunistic infections and septic episodes, thus greatly improving patients' overall survival and disease-free survival. [4-6]

Lymphoproliferative disorders in HIV positive patients often present in hosts with advanced immunosuppression, are associated with infectious complications and significant mortality rates. Co-existing AIDS-defining illnesses in late-presenting HIV-positive individuals may worsen survival. Despite survival rates similar to HIV-negative individuals, HIV-positive patients with diffuse large B cell lymphoma achieved cure rates of 30–50%. [7] Significant differences in prognostic factors like cancer histotype, CD4+ T lymphocyte count (CD4), International Prognostic Index (IPI) or International Prognostic Score (IPS) and antineoplastic chemotherapy protocols have been associated with clinical outcomes. [8-10]

In HIV-negative patients with lymphoproliferative disorders, severe infective complications are generally managed with the aid of granulocyte colony stimulating factors (G-CSF) and the use of prophylaxis for bacterial infections and for *Pneumocystis jirovecii* pneumonia in selected high-risk subjects. [11] For instance *Pneumocystis jirovecii* prophylaxis is recommended in HIV-negative high risk patients including in those with prolonged CD4+ cell count below 200 cell/uL or receiving prolonged steroid treatment. [12]

Standardized and effective strategies for HIV-positive patients are lacking; furthermore widespread concern remains on the selection of fluoroquinolone resistant bacterial strains. [13]

Apart from available clinical trial data and retrospective analyses on AIDS-related lymphomas, there is a substantial lack of information concerning the incidence and the outcomes of infections during the treatment of lymphoproliferative disorders in HIV-positive patients. Although most of the antimicrobial recommendations for lymphoproliferative disorders in HIV-negative subjects can be extended to HIV-positive patients, they may be inadequate to prevent and properly manage the complications of opportunistic infections [namely Cytomegalovirus (CMV), *Toxoplasma gondii* and *Mycobacterium tuberculosis*] in the HIV-positive host. Moreover no guidelines have been established in such settings.

The aim of this study was to characterize the incidence, risk factors and outcomes of infectious complications in HIV-positive patients treated for lymphoproliferative disorders.

Methods

Patient selection and follow up

A retrospective study on adult HIV-positive patients presenting with lymphoproliferative disorders in a single centre between 2000 and 2012 was performed. All consecutive patients were included after revision of their complete medical records within the study period.

Patients were treated at Amedeo di Savoia Hospital (Turin, Italy) by Infectious Diseases consultants, in collaboration with Haematology consultant (working at Città della Salute e della Scienza Hospital, , Turin, Italy). Chemotherapies were administered in the Infectious Diseases ward and patients were discharged according to clinical conditions. Apart from co-trimoxazole (800/160 mg at alternate days) no other primary prophylaxis was administered to study participants. G-CSF was prescribed as per the haematologist team's advice, according to the chemotherapy regimen administered and the degree of myelotoxicity expected and observed. Antiretroviral therapy was started and managed according to international guidelines.

Microbiological analysis

Identification of bacterial, fungal and mycobacterial infections was performed via standard haemocultures, cultures of other samples, or PCR analysis. Viral infections were diagnosed via detection of viral DNA in muco-cutaneous swabs (HSV and VZV) or CMV DNA in serum. CMV infection/reactivation was defined as a febrile illness without other plausible cause, and detectable CMV DNA; CMV end-organ disease was defined as evidence of organ disease with CMV-associated clinical or histopathological characteristics and detectable CMV DNA. [15] *Pneumocystis jirovecii* pneumonia was defined as an acute interstitial pneumonia with positive *Pneumocystis jirovecii* on bronchoalveolar lavage, and absence of other causes for pneumonia. Diagnoses of neurotoxoplasmosis was based on clinical, radiological and microbiological criteria. Plasma HIV RNA was measured through real-time PCR with 2 different assays: Cobas Amplicor HIV-1 Monitor test, version 1.5 until 2008 (limit of detection of 50 copies/mL) and CAP/CTM Roche Taqman 2.0 (limit of detection 20 copies/mL, 2008-2012).

Sepsis was defined as the presence of bacteraemia, in association with criteria for the diagnosis of systemic inflammatory response syndrome.

Statistical analysis

Demographic, immunological, virological and therapeutic data were described and correlated to the incidence of infections with patients' survival. Kaplan-Meyer curves (with log-rank test) and Cox proportional hazard model were used to analyse factors associated with time-updated incidence of infections and survival. A forward step-wise selection method was used in order to select the relevant predictive variables. The following factors were analysed as infection predictors: age (per 10 years increase), gender, anti-HCV positivity, previous AIDS, current AIDS, CD4+ cell count at diagnosis, HAART prior to lymphoma diagnosis, viral load below 50 copies/mL at diagnosis, IPI/IPS score, lymphoma stage, rituximab use, persistent neutropenia (neutrophil count below 500/uL for more than 7 days), protease inhibitor (PI)-based HAART during chemotherapy (vs other antiretroviral treatments), type of lymphoma (NHL vs HD vs BL).

148 For the multivariate survival analysis all the aformentioned factors were included, as well as the
149 emergence of infections and of cytomegalovirus reactivation. All statistical analyses were performed
150 with the Statistical Package for Social Sciences ver. 20.0 (IBM Corp. Released 2011. Armonk, NY:
151 IBM Corp). Data are expressed as medians (interquartile range).
152
153 **Results**
154 **Baseline characteristics**
155 One hundred and three patients were included: they were mostly male (81, 78.6%), Caucasians (101,
156 98.1%), aged 43 years (39-51). Estimated duration of HIV infection was 5.1 years (0.2-13.2): 22
157 patients (21.2%) had a previous diagnosis of AIDS while 29 subjects (27.9%) were presenting with
158 AIDS. Median CD4+ cell count was 138/uL (45-311); 19 patients (18.4%) had an undetectable viral
159 load (below 50 copies/mL) at time of lymphoma diagnosis. Fifty-eight patients (56.3%) had NHL,
160 thirty-two patients had HL (29.1%), and ten patients, (9.7%) had BL; 2 patients had low-grade B
161 cell lymphomas, and one a polyclonal B lymphocytes proliferation. Tumor staging was of stage IV
162 in n=74 patients (71.8%) and stage III in 7 patients (6.8%); IPI/IPS score was above 2 in 54.4% of
163 patients. Baseline demographic, immunological, virological and neoplastic characteristics are shown
164 in table 1, in correlation with lymphoma histopathology.
165 Patients with NHL received the following antineoplastic chemotherapy: cyclophosphamide/
166 doxorubicin/vincristine/prednisone ("CHOP": n =41, 70.7%), cyclophosphamide/doxorubicin/
167 etoposide ("CDE": n =3, 5.2%), adriamicin/prednisolone/vincristine ("APO", n =2, 3.4%) and
168 mesna/ifosfamide/novantrone/etoposide ("MINE", n =2, 3.4%). HL were treated with
169 adriamicin/bleomycin/vinblastine/dacarbazine ("ABVD", 24, 75%), Stanford V (3, 9.4%) and
170 etoposide/epirubicin/bleomycin/cyclophosphamide/prednisolone ("VEBEP", 2, 6.2%).
171 Patients with BL received chemotherapy with CODOX-M/IVAC regimens (n =8, 80%) containing
172 cyclophosphamide/vincristine/doxorubicin/high-dose-methotrexate plus ifosfamide/etoposide/high-
173 dose-cytarabine.

Rituximab was administered to 34 patients (58.6%) with NHL and 2 patients (20%) with BL, respectively. Antineoplastic chemotherapy doses were reduced in 13 patients (12.6%).

Antiretroviral treatment was administered concomitantly with chemotherapy in 89 patients (86.4%): anti-HIV regimens were mostly PI-based (64, 71.9%), non nucleoside reverse transcriptase inhibtor (NNRTI)-based (19, 21.3%), or raltegravir-based (6, 6.7%).

Incidence and time course of infections

Patients contributed to 503 person-years: 44 patients (42.7%) developed 82 infections in the first three years after the diagnosis of lymphoma. The reported infections were caused mostly by bacteria (35, 42.7%), followed by viruses (28, 34.1%), mycobacteria (7, 8.5%), protozoa (7, 8.5%) and fungi (5, 6.1%); specific aetiologies are reported in table 2.

Infections were reported 61 days (1-148) after the lymphoma diagnosis: bacterial, viral, fungal, protozoal and mycobacterial episodes were reported after 63 days (14-154), 80 days (9-149), 1 day (1-180), 103 (1-145) and 21 (0-70), respectively (figure 1).

At univariate analysis a CD4+ cell count below 100/uL at baseline (p=0.02), not receiving HAART (p=0.01), prolonged neutropenia (p=0.001) and rituximab use (p=0.02) were associated with the occurrence of infections. Not being on HAART at diagnosis [p=0.012, adjusted odds ratio ("aOR") 3.45, 95%CI 1.30-9.11] and rituximab use (p=0.014, aOR 3.52, 95%CI 1.28-9.66) were independently associated with the occurrence of infection, in a multivariate Cox-proportional hazards model.

CMV reactivation emerged 53 days (13-156) after the lymphoma diagnosis, with a median CMV DNA of 10357 copies/mL (4350-31076): 5 cases of end-organ disease were diagnosed (4 retinitis, 1 gastrointestinal). The same factors were investigated as predictors for CMV reactivation: at univariate analysis a CD4+ cell count below 100/uL at diagnosis (p=<0.001, OR 15, 95%CI 4.2-53.4), HAART use before diagnosis (p=0.001), viral load below 50 copies/mL at diagnosis (p=0.03), prolonged neutropenia (p=0.004) and rituximab use (p=0.03) were associated with the occurrence of infection.

At multivariate analysis the only independent predictor of CMV reactivation was a CD4 cell count below 100/uL at diagnosis (p=0.001, aOR 23.5, 95%CI 3.70-147.00).

Survival

Sixty-five patients (63.1%) survived: five year survival was higher for HL (78.1%) versus NHL (58.6%) and BL (50%) (p=0.023, log-rank test). Median overall survival was 1430 days (196-2786): it was longer for HL 1781 days (720-3839) versus NHL 1540 days (191-2845) and BL 482 days (52-2847) (log-rank test p=0.001, figure 2a).

Univariate (log-rank test) and multivariate analysis (Cox proportional hazard model) are described in table 3. Once corrected a IPI/IPS score above 2 (p=0.004, aOR 6.549, 95% CI 1.80-23.85) and CMV reactivation (p=0.032, aOR 2.74, 95% CI 1.090-6.87) were independently associated with increased mortality risk (figure 2b and 2c).

Discussion

In this retrospective study of HIV-positive patients diagnosed with lymphoproliferative disorders a significant incidence of infections (16.3 case for 100 person-years) was observed; nevertheless overall survival was similar to other case-series (and better for Hodgkin's lymphomas). [16,17]

This study has several limitations: its retrospective design, the heterogeneous histopathologic patterns and antineoplastic chemotherapies used, the large time frame (11 years with different treatment possibilities), varied combinations of antiretroviral therapies as well as the different management of incident infections. One of the major limitations of the study is the small sample size with limited power for assessing secondary objectives (evidenced by wide confidence intervals at multivariate analysis). It should be taken into consideration that routine hospital admission for antineoplastic chemotherapies may have increased the incidence of bacterial and fungal infections (often health care-associated); on the other hand patients had no antimicrobial prophylaxis except for co-trimoxazole as primary prevention of Pneumocystis pneumonia. We should also acknowledge that

additional factors (unreported comorbidities or medications, chemotherapy delays or modified dosing, etc.), not taken into account, might have influenced the observed results.

The emergence of HIV-associated infections (such as toxoplasmosis, Pneumocystis pneumonia and CMV reactivation) suggests that specific guidelines for the management and prophylaxis of opportunistic infections in this cohort are warranted. Antibacterial prophylaxis in patients treated for lymphomas is generally recommended following evidence from systematic reviews [11], and it may be applied to HIV-positive patients. Some experts advise caution in this approach due to the possible selection of resistant strains: we did not have complete data on antimicrobial sensitivity (apart from one case of multi-resistant *Pseudomonas aeruginosa* and one *Acinetobacter baumannii*, and one methicillin-resistant *Staphylococcus aureus*). Infections were less common in patients establishedon HAART before lymphoma diagnosis and with no rituximab in their antineoplastic regimens.

A multi-centre clinical trial assessing the addition of rituximab to CHOP [18] on 105 HIV-positive patients with NHL reported an increased risk of death in the group randomized to rituximab plus CHOP (RCHOP): 14% of the patients receiving R-CHOP had infective complications secondary to treatment while 2% in the group randomized to standard CHOP regimen. This is in contrast with a recent meta-analysis; although the observations did not reach statistical significance an advantage of rituximab-containing regimes in terms of overall response rate, complete response rate and 2-year overall survival rate was observed. [6, 19]

Focusing on the incidence of infections and their associated mortality, patients with high IPI/IPS scores and low CD4+ cell count were found to be at higher risk of developing infectious complications: in the aforementioned clinical trial 60% of the deaths were in patients with a lymphocyte CD4+ cell count below 50 cells/uL. [14, 15, 19,20] This is consistent with data from other studies showing that low CD4+ cell count is associated with an increased risk of bacterial infections in HIV-positive neutropenic patients, probably due to abnormalities in neutrophil response. [21,22] Data from a trial (BURKIMAB study) conducted on 118 patients with BL treated with intensive immune-chemotherapy (n =37 HIV-positive) showed no statistically significant differences

252 in any response parameters between HIV-positive and negative patients; nevertheless early death
253 (mainly due to infections) was more frequent in the HIV-positive group. [24]
254 Seven mycobacterial infections were observed, which further complicated the management of both
255 antiretroviral and antineoplastic regimens. Interferon-gamma release assays for the detection of latent
256 tuberculosis in HIV-positive patients [24,25] may be particularly advised in patients with lymphoma,
257 given the higher risk of mycobacterial reactivation. Nevertheless data on the treatment of latent
258 tuberculosis in HIV-positive patients with lymphoproliferative disorders are not available.
259 We observed a high incidence of CMV reactivation (3.5 cases per 100 patient-years), which is a
260 potential concern. In patients with NHL (considering 17 trials and one single case report) 15 cases of
261 CMV-associated end-organ disease (on 1566 included patients) emerged: however CMV reactivation
262 may have been underreported in such studies and in studies on HIV-associated HL. [16,17, 26-38]
263 Apart from serious end-organ complications (retinitis and gastroenteritis) CMV viremia has been
264 associated with reduced survival in HIV-positive patients without neoplastic disorders. [39-41] In our
265 cohort the only predictor of CMV reactivation was a CD4+ cell count below 100 cells/uL at diagnosis,
266 with an adjusted odds ratio of 15.5. Furthermore the occurrence of CMV reactivation during the
267 course of chemotherapy was significantly associated with reduced survival. These observations may
268 warrant prospective studies aimed at identifying the best management of HIV-positive patients with
269 lymphomas: pre-emptive approaches and primary prophylaxis should be investigated. Furthermore
270 CMV reactivation may be associated with poor immune recovery and a delay in HIV control: recent
271 data suggest that an early virological response to antiretroviral treatment is significantly associated
272 with improved survival. [42]
273 HIV-positive patients with lymphoproliferative disorders have a high incidence of infections which
274 has been associated with poor baseline immune status and rituximab use. Given the association
275 between survival and infections occurrence (specifically of CMV reactivation) clinical practice
276 guidelines for the prophylaxis and management of infectious episodes during the course of
277 chemotherapy are warranted.
278

Compliance with Ethical Standards:

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Figure legends

448 **Figure 1.**Emergence of incident infections over time (Log10 days). Central line and brackets
449 represent medians and interquartile ranges. Symbols on the y axis represent patients presenting with
450 concomitant infections and lymphomas.
451
452 **Figure 2.**Kaplan Meier curves stratified according to lymphoma type (I), reactivation of CMV (II)
453 and IPI/IPS score at baseline (III).
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