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

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(Article begins on next page)

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

3
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40

41 **Abstract**

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

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

47 **Methods:** A retrospective study in HIV-positive adults with lymphoproliferative disorders (2000-
48 2012). Patients were hospitalised to receive antineoplastic chemotherapy; as well as antimicrobial
49 prophylaxis with alternate day co-trimoxazole (800/160 mg).

50 **Results:** 103 patients were included: mostly males (81, 78.6%), Caucasians (101, 98.1%), with a
51 median age of 43 years (39-51). Fifty-eight (56.3%) patients had non-Hodgkin's lymphoma (NHL),
52 thirty-two (29.1%) had Hodgkin's lymphoma (HL) and ten patients (9.7%) had Burkitt's lymphoma
53 (BL). Five year survival was 63.1%: the best survival rates were reported in HL (78.1%), followed
54 by NHL (58.6%) and BL (50%). Forty-four patients (42.7%) developed 82 infections during follow
55 up: identified causative agents were bacteria (35, 42.7%), viruses (28, 34.1%), mycobacteria (7,
56 8.5%), protozoa (7, 8.5%) and fungi (5, 6.1%). Cytomegalovirus infections (n=17, including 5 end-
57 organ diseases) emerged 53 days after the diagnosis: multivariate analysis showed CD4+ cell count
58 <100/uL as the only independently associated factor (p<0.001, aOR=23.5). Two factors were
59 associated with mortality risk: a IPI/IPS-score of >2 (p=0.004, aOR=6.55) and the presence of CMV
60 disease (p=0.032, aOR=2.73)..

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

64

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

66

67 **Introduction**

68 HIV-positive patients have an increased risk of lymphoproliferative disorders compared to the non-
69 infected population. Standardized incidence rates for NHL are reported to be 103 (88.8-119) in the
70 pre Highly Active Antiretroviral Treatment (HAART) era (1985-1996), 26.7 (19.9-35.1) in the early
71 HAART era (1997-2001) and 16.2 (11.1- 22.9) in the late HAART era (2002-2006). [1] Conversely
72 Hodgkin's lymphoma standardized incidence rates seemed to increase in the late HAART era (from
73 9.2 to 28.1), accounting for the second most common non-AIDS defining cancer. [1,2] Before the
74 introduction of HAART outcomes in HIV positive patients with lymphomas were very poor, mainly
75 due to the failure of chemotherapy regimens and the development of opportunistic and non-
76 opportunistic infections (with sepsis being frequently reported). [3]

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

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

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

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

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

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

106

107 **Methods**

108 **Patient selection and follow up**

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

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

120

121 **Microbiological analysis**

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

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

136

137 **Statistical analysis**

138 Demographic, immunological, virological and therapeutic data were described and correlated to the
139 incidence of infections with patients' survival. Kaplan-Meier curves (with log-rank test) and Cox
140 proportional hazard model were used to analyse factors associated with time-updated incidence of
141 infections and survival. A forward step-wise selection method was used in order to select the relevant
142 predictive variables. The following factors were analysed as infection predictors: age (per 10 years
143 increase), gender, anti-HCV positivity, previous AIDS, current AIDS, CD4+ cell count at diagnosis,
144 HAART prior to lymphoma diagnosis, viral load below 50 copies/mL at diagnosis, IPI/IPS score,
145 lymphoma stage, rituximab use, persistent neutropenia (neutrophil count below 500/uL for more than
146 7 days), protease inhibitor (PI)-based HAART during chemotherapy (vs other antiretroviral
147 treatments), type of lymphoma (NHL vs HD vs BL).

148 For the multivariate survival analysis all the aforementioned 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.

174 Rituximab was administered to 34 patients (58.6%) with NHL and 2 patients (20%) with BL,
175 respectively. Antineoplastic chemotherapy doses were reduced in 13 patients (12.6%).
176 Antiretroviral treatment was administered concomitantly with chemotherapy in 89 patients (86.4%):
177 anti-HIV regimens were mostly PI-based (64, 71.9%), non nucleoside reverse transcriptase inhibitor
178 (NNRTI)-based (19, 21.3%), or raltegravir-based (6, 6.7%).

179

180 **Incidence and time course of infections**

181 Patients contributed to 503 person-years: 44 patients (42.7%) developed 82 infections in the first three
182 years after the diagnosis of lymphoma. The reported infections were caused mostly by bacteria (35,
183 42.7%), followed by viruses (28, 34.1%), mycobacteria (7, 8.5%), protozoa (7, 8.5%) and fungi (5,
184 6.1%); specific aetiologies are reported in table 2.

185 Infections were reported 61 days (1-148) after the lymphoma diagnosis: bacterial, viral, fungal,
186 protozoal and mycobacterial episodes were reported after 63 days (14-154), 80 days (9-149), 1 day
187 (1-180), 103 (1-145) and 21 (0-70), respectively (figure 1).

188 At univariate analysis a CD4+ cell count below 100/uL at baseline (p=0.02), not receiving HAART
189 (p=0.01), prolonged neutropenia (p=0.001) and rituximab use (p=0.02) were associated with the
190 occurrence of infections. Not being on HAART at diagnosis [p=0.012, adjusted odds ratio (“aOR”)
191 3.45, 95%CI 1.30-9.11] and rituximab use (p=0.014, aOR 3.52, 95%CI 1.28-9.66) were
192 independently associated with the occurrence of infection, in a multivariate Cox-proportional hazards
193 model.

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

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

202

203 **Survival**

204 Sixty-five patients (63.1%) survived: five year survival was higher for HL (78.1%) versus NHL
205 (58.6%) and BL (50%) (p=0.023, log-rank test). Median overall survival was 1430 days (196-2786):
206 it was longer for HL 1781 days (720-3839) versus NHL 1540 days (191-2845) and BL 482 days (52-
207 2847) (log-rank test p=0.001, figure 2a).

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

212

213 **Discussion**

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

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

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

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

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

244 Focusing on the incidence of infections and their associated mortality, patients with high IPI/IPS
245 scores and low CD4+ cell count were found to be at higher risk of developing infectious
246 complications: in the aforementioned clinical trial 60% of the deaths were in patients with a
247 lymphocyte CD4+ cell count below 50 cells/uL. [14, 15, 19,20] This is consistent with data from
248 other studies showing that low CD4+ cell count is associated with an increased risk of bacterial
249 infections in HIV-positive neutropenic patients, probably due to abnormalities in neutrophil response.
250 [21,22] Data from a trial (BURKIMAB study) conducted on 118 patients with BL treated with
251 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

279

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290

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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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