Retrospective study

A retrospective study to evaluate the activity of the interferon-free regimens during or after immune-chemotherapy in patients with hepatitis C virus-associated diffuse large B-cell lymphoma

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HCV-DLBCL-IFN-free-2016

STUDY COORDINATOR

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BACKGROUND

In addition to liver involvement, hepatitis C virus (HCV) infection has been linked to the development of type II mixed cryoglobulinemia and to a spectrum of lymphoproliferative disorders (Saadoun 2007). Systematic reviews of studies evaluating prevalence of HCV infection in B-cell non-Hodgkin lymphomas (B-NHL) concluded that HCV prevalence in patients with B-NHL is higher with respect to general population, thus suggesting a role of HCV in the etiology of B-NHL (Dal Maso 2006). Moreover, many epidemiological studies have increasingly strengthened the evidence that HCV is associated not only with indolent B-cell non-Hodgkin lymphomas (NHL), but also with diffuse large B-cell lymphomas (DLBCL). For example, an Italian case-control study reported an even higher association of HCV infection with DLBCL (Odds Ratio [OR] 3.5) with respect to indolent NHL (OR 2.3), suggesting that approximately one out of 20 cases of DLBCL, at least in Italy, may be attributable to HCV (Mele 2003). Similarly, in a large international subtype-specific analysis, HCV prevalence was significantly associated with diffuse large B-cell lymphoma (DLBCL) as well as marginal zone lymphoma (MZL), and lymphoplasmacytic lymphoma (LPL) (de Sanjose 2008). From the pathogenetic point of view HCV-associated DLBCL cases are frequently transformed from MZL: at this regard a recent study demonstrated that, differently from HCV-negative cases, patients with HCV-positive DLBCL display mutations of NOTCH pathway in up to 26% of cases, a mutational signature typical of splenic marginal-zone lymphomas (SMZL), and that NOTCH mutations are significantly associated with low grade component in the diagnostic biopsy and with a poor outcome (Arcaini 2015).

Unlike indolent B-NHL (Hermine 2002; Arcaini 2014), there seems to be no role for antiviral treatment (AVT) as a single curative approach in HCV-positive DLBCL, because lymphoma cells, suffering from additional oncogenic lesions, may not be critically dependent on antigen stimulation. For this reason, unlike their indolent counterpart, HCV-associated DLBCL patients should be treated with conventional immune-chemotherapy schemes such as R-CHOP, although concerns remain with regard to the potential risk of hepatotoxicity. In a large retrospective study on 232 patients carried out by Fondazione Italiana Linfomi (FIL) the prognosis of HCV-positive DLBCL treated with R-CHOP seemed to be relatively good, with 3-year PFS of 58% and 3-year OS of 71%; severe hepatic toxicity was 16%. This study developed a new multivariable prognostic model ("HCV Prognostic Score", HPS), based on 3 readily available factors (performance status, albumin level and HCV-RNA viral load), that was able to identify 3 risk-categories with different survival in HCV-associated DLBCL Merli 2014). A prospective French observational study (ANRS HC-13 Lympho-C) showed a similar prognosis in 45 patients treated with R-CHOP (3-year OS 73%) (Michot 2015).

In the interferon era very few reports described the use of AVT after immune-chemotherapy in patients with HCV-positive DLBCL, although scanty retrospective data seem to suggest a possible benefit on survival. For example in the FIL study, the 23 patients who received AVT after R-CHOP demonstrated an improved OS with respect to those that did not receive it (Merli 2014). Moreover in the French ANRS HC-13 Lympho-C study, the 17 patients who received AVT after showed a borderline benefit on PFS and OS (P = 0.06) (Michot 2015). This may be due to the reduction of long-term progression to cirrhosis and hepatic events and to the eradication of a possible trigger of lymphoma relapse involving a potential low-grade clone.

The advent of new direct-acting antiviral agents (DAA), that are associated with a >90% rate of HCV eradication across all genotypes, may increase the appealing and the frequency of AVT administration after R-CHOP. Moreover, in selected cases in which the administration of R-CHOP may be difficult due to the development of severe liver toxicity, the rapidity of action and the absence of significant side-effects of DAA may allow the completion of immune-chemotherapy

and the achievement of complete response (CR) also in cases with more advanced hepatic disease. Data on new interferon-free regimens in HCV-associated DLBCL are scanty and based on clinical reports (Carrier 2015). With the present study we plan to collect data on patients with DLBCL and HCV infection treated with new regimens in order to obtain data on PFS and OS in this setting; in particular we plan to compare these data with historical cohorts treated with R-CHOP without concurrent or subsequent AVT.

OBJECTIVES

Primary Objectives

- Hematological: to investigate the efficacy of interferon-free regimens on progression-free survival (PFS) in HCV-associated DLBCL
- Virological: to evaluate the efficacy of interferon-free regimens to eradicate HCV infection in patients with DLBCL

Secondary Objectives

- Hematological: to investigate survival rate in patients with HCV-associated DLBCL
- Safety of treatment with interferon-free regimens following immune-chemotherapy in HCV-associated DLBCL
-Feasibility and safety of concurrent interferon-free regimens and immune-chemotherapy in HCV-associated DLBCL
-Causes of death

ENDPOINTS

Primary endpoints

- 2-year PFS, defined as the time between enrolment and progression or relapse or death from any cause.
- Sustained virological response (SVR) after interferon-free regimens following or concurrently with immune-chemotherapy

Secondary endpoints

- 2-year event-free survival (EFS) defined as time between enrolment and failure of treatment or death as a result of any cause.
- 2-year overall survival (OS) defined as the time between enrolment and death from any cause.
- Toxicity of interferon-free regimens, either subsequent or concurrent to immune-chemotherapy; toxicity will be classified according to definitions of Common Terminology Criteria for Adverse Event version 4.03 (CTCAE). It will be determined by the incidence of severe, life- threatening (CTCAE grade 3, 4 and 5) and/or serious adverse events.

STUDY DESIGN

Retrospective multicentre study. Patients with DLBCL associated with HCV infection (HCV-RNA positive) will be enrolled.
The study includes patients treated with interferon-free regimens.

STATISTICAL ANALYSIS

Due the retrospective characteristic of the study, we did not plan a sample size, however we estimate to collect data on 30-40 patients in national and international centers. Given that HCV-positive is a rare disease and that IFN-free antiviral regimens have been rarely used in this setting

so far, all patients with HCV-positive DLBCL consecutively treated with IFN-free regimens have to be considered and included in the study.
PET-based response criteria according to "Lugano Classification" (Cheson et al, JCO 2014) will be adopted. Sustained virological response (SVR) will be defined as undetectability of HCV RNA according to the RT-PCR of each Centre 12 weeks after completion of AT.
Overall Survival (OS) will be defined with the time from lymphoma diagnosis since the last follow-up or death for any cause. Progression-free survival (PFS) was measured from lymphoma diagnosis to relapse or death. Event-free survival (EFS) defined as time between enrolment and failure of treatment or death as a result of any cause.
Categorical variables will be described by count and relative frequency (%) of each category. Numerical variables will be summarized by their median and range. Association between categorical variables will be evaluated by Fisher's exact test. Survival curves have been calculated by using the Kaplan-Meier product-limit method and the comparisons of survival curves between groups of patients was carried out by log-rank test.

PATIENT SELECTION CRITERIA
Patients with diffuse large B-cell lymphoma (DLBCL) associated with HCV infection (HCV-RNA positive) will be enrolled.
The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. The following items are generally used in the definition of selection (eligibility) criteria:

1.1 Inclusion criteria
1. Age > 18 years
2. Diffuse large B-cell lymphoma (DLBCL)
3. HCV-RNA positivity
4. Treatment with interferon-free regimens either concurrent or subsequent to immune-chemotherapy regimens

1.2 Exclusion criteria
1. HIV-positivity
2. CNS disease (meningeal and/or brain involvement by lymphoma)

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