Interim PET Response-adapted Strategy in Untreated Advanced Stage Hodgkin Lymphoma: Results of GOELAMS LH 2007 Phase 2 Multicentric Trial

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Abstract

Hodgkin lymphoma is a curable disease with outcomes depending on initial prognostic factors and interim treatment response. Here, we conducted a phase II trial in advanced stage Hodgkin lymphoma to assess the feasibility and efficacy of a positron emission tomography-adapted strategy with early salvage for poor metabolic responders. We show that this strategy is feasible and leads to interesting results for the whole population.

Background: Patients with advanced stage Hodgkin lymphoma still present unsatisfactory outcomes. **Patients and Methods:** The Groupe d'étude des Leucémies Aigues et des Maladies du Sang (GOELAMS) group conducted a prospective multicentric trial (NCT00920153) for advanced stage Hodgkin lymphoma to evaluate a positron emission tomography (PET)-adapted strategy. Patients received an intensive regimen (VABEM [vindesine, doxorubicin, carmustine, etoposide, and methylprednisolone]) in front-line and interim ^{18F}FDG-PET evaluation after 2 courses (PET-2). Patients with negative PET-2 findings received 1 additional course. Patients with positive PET-2 findings underwent early salvage therapy followed by high-dose therapy/autologous stem cell transplantation. **Results:** Fifty-one patients were included. The final complete remission rate was 88%. With a median follow up of 5.3 years, 5-year event-free survival and overall survival rates were 75.3% and 85.3%, respectively, for the whole cohort. Patients who were PET−2-negative had 5-year event-free survival and overall survival rates of, respectively, 77.8% and 88.2% versus 85.1% and 91.7% for patients who were PET−2-positive. **Conclusion:** A PET-guided strategy with early salvage therapy and high-dose therapy/autologous stem cell transplantation for patients with interim PET−2-positive findings is safe and feasible and provide similar outcome as patients with a negative PET-2.

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Introduction

Continuous improvements in the management of Hodgkin lymphoma (HL) has resulted in favorable outcomes for most patients. A combination of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) and radiotherapy has long been considered as standard treatment for HL but fails to cure 20% to 30% of patients with advanced stage disease.[1-3] To improve results for patients with advanced stage disease, new regimens have been developed with an

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increased dose intensity compared with the ABVD regimen. The German Group promoted escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) ($_{esc}$BEACOPP) with good results in term of event-free survival (EFS).[2-5] In the same way, the "Groupe d'étude des Leucémies Aigues et des Maladies du Sang" (GOELAMS) developed an intensive regimen called VABEM (vindesine, doxorubicin, carmustine, etoposide, and methylprednisolone) in the 1990s.[6] In the H97-HR trial, 3 courses of VABEM as frontline therapy were compared with 4 cycles of ABVD followed by autologous stem cell transplant (ASCT) and showed similar complete remission (CR) rates and 5-year overall survival (OS) (85.9%-87%).[7] Despite a better tumoral control with intensive regimens, the benefit in OS is less clear, probably owing to late toxicities and the efficacy of a second-line regimen for patients progressing after ABVD, whereas salvage therapy after $_{esc}$BEACOPP seems less reliable.[8] Furthermore, some authors pointed out that these intensive strategies lead to overtreatment for a large proportion of patients who are good responders.

One remaining challenge is to identify patients who will not achieve durable remission with standard front-line treatment to propose adapted therapy. Early functional imaging ^{18F}-Fluorodeoxyglucose positron emission tomography (^{18F}FDG-PET) has a good prognostic value on final response rate and OS. A positive interim PET/CT is especially a strong predictor of unfavorable outcomes.[9-12] More recently, the results of interim PET have been integrated into risk-adapted treatment schedules.[13-16]

Based on the previous results of the VABEM regimen, in 2008, the GOELAMS group conducted a prospective multicentric trial integrating interim PET results for patients with advanced HL with very poor prognoses. This trial was designed to allow short intensive therapy for early good metabolic responders and a salvage therapy followed by high-dose therapy (HDT)/ASCT for non-early responders.

Patients and Methods

This prospective open-label multicenter phase 2 trial was registered with clinicaltrials.gov (NCT00920153) and approved by the Grenoble University Hospital ethics committee. All patients were included between June 9, 2008 and January 28, 2010 and provided written informed consent before study entry.

Patients

Patients with newly histologically proven HL (age range, 18-65 years) were included and stratified according to the GOELAMS Prognostic Score System (PSS) based on age ($\leq$ 40 years = 0; $>$ 40 years = 1), number of involved nodes (0-2 = 0; 3-5 = 1; $\geq$ 5 = 2), and B symptoms (absence = 0, presence = 1) into favorable, intermediate, or advanced (PSS $\geq$ 4) stage HL.[17] All patients with PSS $\geq$ 4 were included in this treatment arm. Pretreatment evaluation included medical history, physical examination, computed tomography (CT) scans of the neck, chest, and abdomen, ^{18F}FDG-PET-CT (PET-0), bone marrow biopsy, serum chemistry, blood cell count, lung function test, and a functional cardiac evaluation. Patients with prior human immunodeficiency virus or viral B or C hepatitis were excluded.

Study Design

VABEM included vindesine 1 mg/m^2 (days [D] 1-5), adriamycin 33 mg/m^2 (D1-3), carmustine (BCNU) 140 mg/m^2 (D3), etoposide 200 mg/m^2 (D3-5), and methylprednisolone 120 mg/m^2 (D1-5); repeated on day 28 (Figure 1). Primary prophylaxis against neutropenia with pegylated granulocyte colony-stimulating factor was mandatory at D6. Treatment was postponed until recovery of neutrophil and platelet counts of at least 1 G/L and 80 G/L respectively. Interim PET (PET-2) was performed after 2 courses of VABEM. Patients with complete metabolic remission underwent a third course. Patients with positive PET-2 were switched to salvage therapy of 3 courses of PDG (cisplatin, gemcitabine, and dexamethasone) followed by HDT and ASCT. PDG included cisplatin 33 mg/m^2 (D1-3), gemcitabine 1000 mg/m^2 (D1 and D8), and dexamethasone 40 mg (D1-4), and peripheral blood stem cell collection was performed between the first and the second PDG course (Figure 2). Patients in metabolic response after 2 courses of PDG received a BEAM (carmustine, etoposide, cytarabine, and melphalan) conditioning regimen, whereas patients who were PET-positive received a MINE-R (mesna, ifosfamide, mitoxantrone, etoposide, and rituximab) regimen before HDT (Figure 1). Involved fields irradiation (30 Gy, 2 Gy per session for 15 days) was planned only for patients with initial bulky lesions ($\geq$ 5 cm).

Response Assessment

PET-CT scanning recommendations were as follows: 2-dimensional acquisitions from the vertex to the mid-part of the thigh 60 to 90 minutes after intravenous administration. Patients were fasted for $>$ 6 hours, and glycemia was checked before administration. The ^{18F}FDG dose was defined according to the local PET analysis device and the patient's weight using the Noise Equivalent Contrast curve. Acquisition times were 30 minutes (8 bed positions; 3-5 minutes per position). All images were processed using the software provided by the PET-CT machine manufacturer. Images were reconstructed in 3 dimensions to permit transaxial, coronal, and sagittal plane series.

Interim response to treatment was assessed according to visual criteria by a local nuclear medicine physician, as the trial was designed before February, 2007.[18] A negative interim PET (performed the week before the third VABEM course) was defined as the disappearance of all visible initial labeling in PET-CT scans and the absence of new hypermetabolic lesions. All significant persistent FDG uptake superior to the local background was considered as a treatment failure whatever its evolution since beginning treatment. Minimal residual uptake by lesions was always considered as positive to avoid undertreatment. As the Deauville criteria were published while the study was ongoing, all PET−2-positive scans were centrally reviewed according to the Deauville score.[19] The final CR was defined as a complete regression of initially involved sites according to the criteria of Cheson et al.[20]

Pharmacovigilance

All toxicities and serious adverse events (AEs) were prospectively declared to the trial pharmacovigilance unit and classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.