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Kasr Al-Aini Center of Clinical Oncology
NEMROCK

PHASE II PROSPECTIVE RANDOMIZED CLINICAL TRIAL OF
DOXORUBICIN, BLEOMYCIN, VINBLASTINE, AND DACARBAZINE (ABVD)
FOLLOWED BY RADIATION THERAPY (RT) VERSUS ABVD ALONE FOR
STAGES I, II, AND IIIA HODGKIN LYMPHOMA WITH ROLE OF
PROGNOSTIC BIOLOGICAL PARAMETERS
(A prospective hospital based study)

A Thesis

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Abstract

Background and Objectives: The optimal treatment of early-stage Hodgkin lymphoma has been controversial because of the success of several approaches. Concerns regarding radiation toxicities and the previously detected good response to chemotherapy have led some to withhold radiation therapy (RT) for the treatment of stage I , II and IIIA Hodgkin's lymphoma. The aim of This study To determine whether combined modality therapy (CMT) is superior to chemotherapy (CT) alone in early stage Hodgkin's lymphoma patients.

Patients and methods: This was a prospective clinical trial carried in Kasr El Aini Oncology And Nuclear Medicine Centre (NEMROCK) . From February 2007 to June 2011, untreated Hodgkin Lymphoma patients with clinical stages (CSs) IA, IB, IIA, IIB, and IIIA were randomized to 4 cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) alone or 4 cycles of ABVD followed by radiation therapy (RT) (3600) cGy. Patients were tested for pre-treatment sCD30 and IL13 levels. Response rate, disease free survival and overall survival were estimated by the Kaplan-Meier method, and Cox multivariable Regression model was used to analyze trends.

Results: Of 60 patients randomized 30 receive RT after 4 cycles of ABVD; the complete remission (CR) percentage was 83.3% and partial response, 16.7%. For ABVD alone, 73% achieved a CR; 23.3%, a partial response (PR); and 3.3%, disease progression. At 30 months relapse rate, progression free survival (PFS), and overall survival (OS) for ABVD _ RT versus ABVD alone are 16.7% versus 28.4% , 83% versus 60% (P _ .004), and 93.3% versus 90% (P _ .222), respectively (log-rank).

Conclusion: Additional radiotherapy improves response, prevents relapse and increases RFS in patients receiving four cycles of ABVD chemotherapy. Combined modality treatment (ABVD and consolidation radiotherapy) is standard of care. A biological parameter such as serum sCD30 level could be helpful in obtaining a more precise selection of patients suitable for more intensive treatment.

Key Word: ABVD-BLEOMYCIN-VINBLASTINE-RT.

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LIST OF ABBREVIATIONS

ABVD	Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine
ASCO	American Society of Clinical Oncology
BUN	Blood urea nitrogen
BCR	B cell receptor
CALGB	Cancer and Leukemia Group B
CBC	Complete blood count
CCG	Children Cancer Group
CD	Cluster of Differentiation
CR	complete response
CRu	complete remission unconfirmed
cGy	CentiGray
Chemo	Chemotherapy
Chemo-RT	Chemo-radiotherapy
CMT	Combined modality treatment
cHL	Classic Hodgkin Lymphoma
CS	Clinical stage
CT	Computed tomography
CTV	Clinical target volume
DLBCL	Diffuse Large B cell Lymphoma
EBV	Epstein - Barr virus
EBVNA	Epstein - Barr virus Nuclear Antigen
LMP	Latent Membrane Proteins
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EFRT	Extended field radiotherapy
EMA	Epithelial membrane antigen
EORTC	European Organisation for Research and Treatment of Cancer
FDG	Fluro Deoxy Glucose
GC	Germinal Center
GELA	Groupe d'Etude des Lymphomes de l'adulte
GHSg	German Hodgkin's Study Group
GTV	Gross tumor volume
HD	Hodgkin's Disease
HL	Hodgkin's lymphoma
HRS	Hodgkin and Reed-Sternberg
LRCHL	Lymphocyte-rich classic Hodgkin lymphoma
IgV	Imunoglobulin V
IIL	Intergruppo Italiano Linfomi

IL	Interlukin
IPS	International Prognostic Score
JCO	Journal of Clinical Oncology
LFTs	Liver function tests
LN	Lymph node(s)
LND	Lymph node dissection
LP	Lymphocytic Predominant
LVEF	Left ventricular ejection fraction
MHC	Major Histocompatibility Complex
MRI	Magnetic resonance imaging
MRU	Minimal Residual Uptake
NCCN	National Comprehensive Cancer
NCIC	National Cancer Institute of Canada
NEJM	New England Journal of Medicine
NLPHL	Nodular Lymphocyte-Predominant Hodgkin Lymphoma
NPV	Negative Predictive Value
OS	Overall survival
PCR	Polymerase chain reaction
PET	Positron emission tomography
PPV	Positive Predictive Value
PR	Partial response
PS	Performance status
PTV	Planning target volume
RFS	Relapse-free survival
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
sCD30	serum Cluster of Differentiation 30
SUV	Standard Uptake Value
WHO	World Health Organization

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I n t r o d u c t i o n

Introduction

The efficacy of treatment in Hodgkin's lymphoma has improved progressively over the last 35 years. Currently available therapeutic modalities (radiotherapy, chemotherapy or both combined) enable the cure of at least 80% to 85% of treated patients [Yung et al. 2003].

The increase of specific survival and the early age of the patients diagnosed with Hodgkin's lymphoma has resulted in the finding of other severe pathologies occurring with a incidence higher than that observed in population subgroups of similar age. About 46% of patients die from causes not directly related to lymphoma: these include secondary neoplasias, cardiovascular events and other toxicities secondary to the treatment administered [Aleman et al. 2003]. This percentage is even higher in patients with early-stage Hodgkin's lymphoma. Recently, Ng et al reported that late toxicity is the main cause of mortality in patients <50 years diagnosed with stage I or II Hodgkin's lymphoma. In this study, mortality unrelated to lymphoma was twice that directly caused by the disease in patients with early-stage disease and a good prognosis [Ng AK et al. 2002].

Some late toxic deaths are due to the use of alkylating chemotherapeutic agents, most of which are specifically related to the MOPP schedule (mechlorethamine, vincristine, procarbazine and prednisone) or derived compounds. Treatment with alkylating agents without radiotherapy is associated with increased lung cancer risk [Travis et al. 2002]. However, late toxicities leading to higher mortality are attributed to radiotherapy [van Leeuwen et al.

1999]. Those patients irradiated by mantlefield have a risk of suffering myocardial infarction three times higher than patients who receive no myocardial irradiation [Hancock et al 1999].

Far more relevant is the continuous and growing risk of developing a second solid tumor, found in patients treated with radiotherapy: this risk increases for at least 25 years after treatment [van Leeuwen et al.2000]. A populationbased study analyzed 32 591 patients and found a relative risk of 22% of having a second solid tumor 25 years after the diagnosis of Hodgkin's lymphoma [Dores GM et al. 2002]. The magnitude of this problem is even more evident if we consider the risk of developing breast cancer in women that have undergone mantle field irradiation. In this particular case, the relative risk is twice that of the overall population [Dores GM et al. 2002]. However, in women treated under the age of ~25 years, the picture is very different. In this population the absolute excess risk of breast cancer (per 10 000 female patients per year of follow-up) has ranged from 16.7 (for patients followed for less than 14 years) to 169 (follow-up longer than 15 years) [van Leeuwen et al. 1999].

A logical way to avoid the late effects of radiotherapy might be to avoid its use. However, this would require alternative therapies that have a similar efficacy to therapies that include radiotherapy. Furthermore, these alternative treatments should not induce severe or potentially lethal late toxic effects. The results of a small randomized study conducted by the American National Cancer Institute were reported in 1991 [Longo et al. 1991]. This study suggested that the administration of six cycles of MOPP chemotherapy was equally or even more effective than extended field radiotherapy in patients with pathological stage I or II

Hodgkin's lymphoma. However, in a similar Italian trial the survival rate was significantly higher in patients treated with radiation therapy. Acute toxicities, infertility and the risk of myeloid leukemia induced by MOPP schedule led to an overall rejection of this therapeutic alternative [Bilal et al. 1992].

Chemotherapy with the ABVD schedule (doxorubicin, bleomycin, vinblastine and dacarbazine) is the standard treatment for advanced-stage Hodgkin's lymphoma: ABVD has been found to be more efficacious than MOPP [Canellos et al 2002] and less toxic than the 'hybrid' chemotherapy MOPP/ABV (mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin and vinblastine) [Duggan et al. 2003]. Moreover, ABVD does not cause sterility [Viviani et al. 1985], and its potential for inducing second solid or hematological neoplasias seems to be lower than the observed with radiation therapy or MOPP. All these facts also support the use of ABVD schedule in patients with early disease stages with especial view on the duration needed [Valagussa et al. 1982].

AIM OF THE WORK

Aim of work

The aim of the current study is to analyze the efficacy of 4 cycles of chemotherapy (ABVD) with or without irradiation among newly diagnosed Hodgkin's lymphoma patients with stages I ,II , IIIA . The treatment results are to be analyzed in correlation with clinical and biologic prognostic factors aiming at defining a subset of patients deserving more aggressive treatment.