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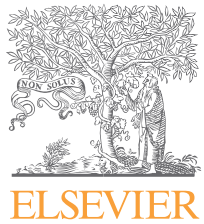

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Clinical achievements of the EORTC Lymphoma Group and aspects of future group strategy

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ABSTRACT

Since1964, the EORTC Lymphoma Group has conducted nine consecutive randomized phase III trials on early-stage Hodgkin lymphoma aimed at increasing efficacy while decreasing short- and long-term toxicities. Event-free and overall survival significantly improved from about 50% and 70%, respectively, in the early years to over 80% and 90%, respectively, more recently. Identification of prognostic subgroups appeared to be a successful method to tailor treatment strategies. Radiotherapy fields have become more restricted whereas chemotherapy has become standard. Early PET-CT has been introduced to investigate the possibility of treatment adaptation. Longitudinal quality-of-life assessment has become an integral part of our studies. An ongoing study focuses on the rehabilitation and quality of long-term survival in all 6658 Hodgkin lymphoma patients treated in EORTC trials since the earliest beginning. In advanced stages overall outcome has improved as well with 10-year survival rates of over 75%.

1. Introduction

The aim of the EORTC Lymphoma Group (LG) is to develop optimal treatment strategies for malignant lymphomas and further to study their natural history, diagnosis, treatment and sequelae of treatment. Until 2006 Hodgkin Lymphoma (HL) as well as Non-Hodgkin Lymphoma (NHL) studies were performed by the group.[1] Due to strong competition of several national NHL groups, it became increasingly difficult to successfully complete NHL clinical trials. Therefore the group changed its strategy and decided to focus mainly on HL for the next years. Successful cooperation has been established with the French *Groupe d'Étude des Lymphomes de l'Adulte* (GELA) and recently with the Italian *Fondazione Italiana Linfomi* (FIL), and there is an active exchange with the *German Hodgkin Study Group* (GHSG).

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2. Achievements of the EORTC Lymphoma Group

2.1. Identification and use of pre-registered initial tumor and patient characteristics as key parameters for adaptation of treatment strategy in localized Hodgkin Lymphoma: 50 years of continuous progress

In the early 1960's, most studies were conducted by Anglo-American academic cooperative groups which were not used to sharing clinical research with the European continent. After Easson had claimed that HL could be cured,[2] clinical research leaders from Belgium, France, Italy, The Netherlands and Sweden decided in 1964 to join forces in the "Radiotherapy-Chemotherapy Cooperative Group" (now Lymphoma Group) and conduct innovative clinical trials.[1] Beside improvement in patient recruitment, the gathering induced close day-to-day work of medical oncologists/hematologists, surgeons, radiation oncologists and pathologists as well as biostatisticians and data managers, a determined attitude that made the EORTC successful. The LG has continuously performed trials over the last five decades to improve the treatment outcome for HL patients. In the period from 1964 to 1988, trials (H1–H6) were aimed at improving immediate results. Among other benefits due to the LG are the deletion of staging laparotomy (H6F trial) as a diagnostic/prognostic procedure and of total nodal irradiation as a standard treatment (H5U). Because of the greatly improved treatment results, later trials were mainly aimed at reducing (late) treatment toxicity while maintaining excellent disease control (H7–H10 for early-stage disease and H34 and the upcoming H11 for advanced disease).[3–5]

The objectives of the first two trials were to improve treatment efficacy. Efforts were made to identify clinical and biological parameters, easy to assess and collect and highly reproducible, that could be used to adapt treatment strategy. Two propagation models of the tumor (the relation of tumor mass to lymphatic spreading and to hematogenous dissemination) and its particular host–tumor relationship were built. The parameters identified were first used to delineate subgroups for which the risk of progression or relapse could be predicted. Actually, the second trial already split patients into two groups of favorable and unfavorable prognosis. Patients being followed up on a regular basis until death, their fate after specific treatments was used to develop strategies to maximize the yield of long-term responses and minimize early and long-term toxicities. These results helped to improve the understanding of other aspects of the management of HL that were relevant for other tumors: the biology of the disease,[6] the response to treatment and its significance, the risk for relapse, the risk for long-term toxicities (secondary malignancies, cardiovascular, pulmonary, digestive and fertility toxicities),[7–11] the quality-of-life considering personal and socio-economic aspects, the improvement in diagnostic procedures and treatment techniques,[12] and in quality assurance and the emergence of decision analysis models.

A major step was attained with the publication of a general stratification algorithm based on just six parameters: age, sex, number of lymph node areas involved, mediastinal bulk, B symptoms, and erythrocyte sedimentation rate.[13] A scoring system was developed and used to identify three prognostic subgroups called very favorable, favorable, and unfavorable. This scoring system was first applied to the H7 trial in which the validity of the definition of the three subgroups was tested, patients belonging to the favorable (F) and unfavorable (U) subgroups being randomized between the appropriate reference treatment and a common experimental treatment.[14] The results demonstrated the usefulness of the scoring system, and it was then applied to subsequent trials. It has also been widely adopted (sometimes with adaptation) for early-stage HL all over Europe and throughout the USA and Canada. In the H8 trial this scoring system was used to differentiate treatment. Involved field radiotherapy (IFRT) was compared to subtotal nodal radiotherapy (STNI) either alone (in F subgroup) or in combination (in U subgroup) with chemotherapy (MOPP-ABV). The results in both arms were in favor of chemotherapy plus IFRT.[15]

Figures 1 and 2 summarize the continuous improvement achieved along the seven trials on early-stage HL for which results are available. It shows that even with limited treatment in low-risk patients, there is room for improvement in treatment efficacy while limiting the risk of long-term treatment related toxicity.

With the availability of new imaging techniques worldwide, the LG has recently completed a large intergroup (GELA, FIL) randomized trial (H10, 2006–2011, 1952 patients) with the objective of testing the concept of early treatment adaptation by assessing clinical response on PET-scan examination after two

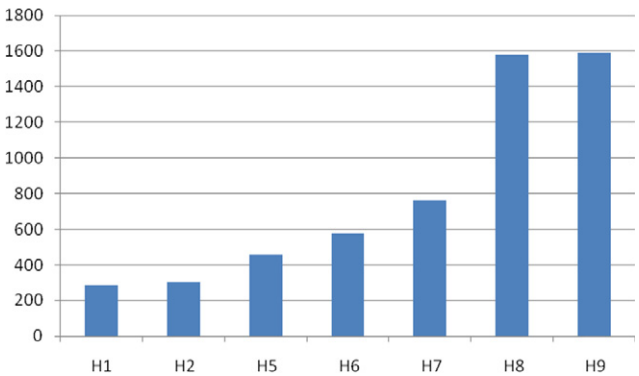

Fig. 1 – Accrual in EORTC Lymphoma Group trials on Hodgkin's Lymphoma clinical stages I and II. H1: 1964–1971; H2: 1972–1976; H5: 1977–1982; H6: 1982–1988; H7: 1988–1993; H8: 1993–1998; H9: 1998–2004.

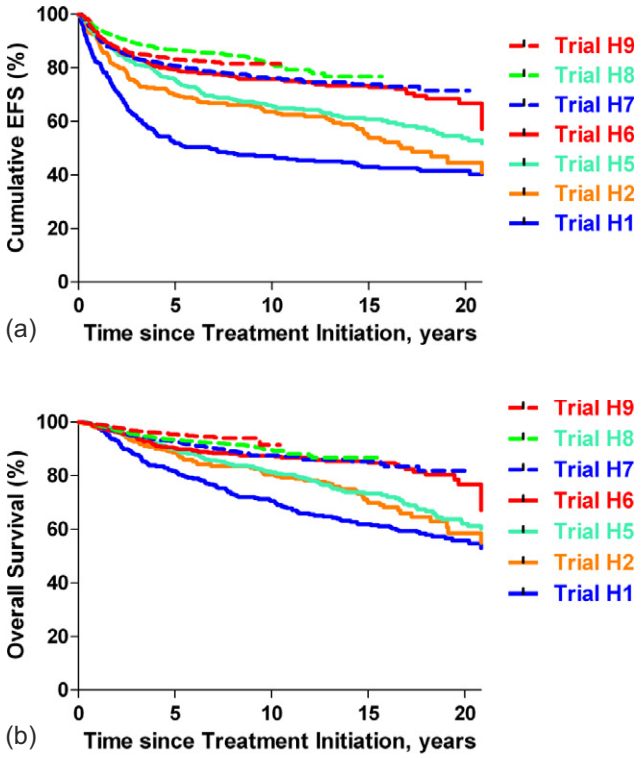

Fig. 2 – (a) Overall cumulative event-free survival by trial (1964–2004; 5,719 patients); (b) Overall survival by trial (1964–2004; 5,719 patients).

cycles of chemotherapy. Also the localization of radiation therapy should be established in the management of patients with early-stage disease as well as the number of chemotherapy cycles needed to induce a stable clinical response. In order to achieve a consensus on the interpretation of early PET scans an internet-based network was built allowing experts to centrally review all scans prospectively.[16] This cooperation gave support for the formation of the EORTC Imaging Group.

In conclusion, the sustained effort that the EORTC-LG placed on rigorous step-by-step analysis resulted in considerable conceptual progress being made in improving survival as well as in avoiding late toxicity.

2.2. Evolution of the LG radiotherapy concepts: from standard to personalized radiation volumes, from lymph node regions to individual involved lymph nodes

When Thomas Hodgkin first described the disease in 1832, it was incurable. After the introduction of local radiotherapy using orthovoltage radiation, the first responses were seen and a small number of patients were cured. Increased knowledge about the spread of the disease and the development of techniques to irradiate larger areas made it possible to cure patients with HL already in the 1960's.[17] Simultaneously, chemotherapy was also developed and multiple combinations of radiotherapy and chemotherapy have been studied ever since.

The concept of delivering radiotherapy to lymph node areas began in 1972. Irradiation to large lymph node areas (either total nodal irradiation, TNI or STNI) was used for over a quarter of a century, from 1972 (H2 trial) through 1998 (H8 trial).[5] In the H9 trial (1998–2004) smaller nodal areas were exclusively irradiated (IFRT). All these radiation fields were based on the Ann Arbor staging of nodal areas. Following the introduction of chemotherapy regimens sufficiently efficient for eradicating microscopic disease and the observation that local recurrences in patients treated with chemotherapy alone were mainly occurring in initially involved lymph nodes,[18] the LG Radiotherapy Subcommittee in 2001 developed the concept of involved node radiotherapy (INRT) for patients with early-stage HL, which was implemented in 2006 in the H10 trial.[19] In addition, the growing evidence of late effects following radiotherapy (dose- and volume-related) also contributed to the reduction of radiation field and dose as much as possible.[4,20,21]

The INRT concept contends that radiotherapy should only be delivered to involved lymph nodes and should encompass the initial lymph node volumes, modified, however, to fit to post-chemotherapy anatomic boundaries often different from the anatomical boundaries prior to chemotherapy.[19] In order for INRT to be delivered safely and in an optimal manner, staging imaging procedures should be of the highest possible accuracy, and the fusion of pre- and post-chemotherapy scanning images should be as precise as possible. Stringent procedures must be established, and all staging images should be acquired with the patient in the same position as that which will be the treatment position. Pre-chemotherapy imaging data should always include contrast-enhanced computed tomography and FDG-PET scans, as these PET scans allow the identification of additional involved nodes in a relatively large number of patients.[12,22,23]

Due to possible difficulties in the superimposition of initially involved lymph nodes onto the post-chemotherapy computed tomography simulation, a prospective quality assurance program should therefore be organized for centers implementing this technique. In France a program has already been implemented in which patient imaging data are exchanged *via* a secured and encrypted internet connection. All French centers are interconnected and can exchange data allowing radiation fields to be prospectively verified in real time.

Further optimization of the INRT concept concerns the reduction of the irradiated volume by using sophisticated radiation delivery techniques[24–26] which allow more conformal therapy and increased sparing of surrounding normal tissues. The INRT concept and its implementation need to be adapted for worldwide use. This

will hopefully be achieved by reaching a consensus in the recently founded International Lymphoma Radiation Oncology Group (ILROG).

In conclusion, the INRT concept is simple and a strongly individualized treatment. It is based on modern imaging and radiation techniques which allow increased sparing of normal tissue. Its implementation requires further improvement in order to achieve greater homogeneity among international groups.

2.3. *Identification and prevention of late toxicity after curative treatment for malignant lymphoma*

The successful treatment of patients with HL and aggressive NHL has resulted in an awareness of long-term therapy-related toxicity in the surviving patients, and the LG was one of the first to address this topic. The memorable meeting held in Paris in 1989, honoring Prof. Tubiana as one of the most important founders of the Group, resulted in a database collected from all over the world consisting of over 14,000 well-documented patients with HL.[27] The survival data from this large cohort were compared with healthy populations matched by sex, age, and country and showed for the first time that HL patients experienced an ongoing excessive death rate years after the end of treatment. The observed to expected ratio of death not related to the disease increased with time from 1.79 in the 0–4 year period after treatment to 3.08 after 15 years and beyond. Major causes of late death were related to secondary malignancies, cardiovascular events, and infections with cumulative risk exceeding that of death from HL 15 years and beyond after treatment.[3,4,27]

For many years, the LG has collected data related to late toxicity in HL patients. Here, not only potential lethal toxicity was studied, but also causes of late morbidity. Extensive data on hormonal abnormalities (thyroid, gonadal), pulmonary function, cardiac function, and also quality-of-life were analyzed.[10,11,28]

Studying HL patients for late therapy-related morbidity and mortality is relatively easy given the young age and high survival rates. In such patients the incidence and prevalence of confounding co-morbidity is far less than in patients with aggressive NHL. As a consequence, analysis of late toxicity had only rarely been performed in small numbers of NHL patients. The LG succeeded in retrospectively analyzing a cohort of 757 NHL patients who were treated in the 1980's and 1990's, and they focused on late morbidity and mortality. This study required effort to collect appropriate morbidity and mortality data with the help of national cancer registries and the Nijmegen cardiovascular morbidity registry. Using competing risk models, it appeared that – after careful correction for the already high prevalence of cardiovascular diseases and malignancies in a population over the age of 50 – the excess of additional cardiovascular events was very high. The standardized incidence ratio of chronic heart failure was markedly increased (SIR = 5.4, 95% CI 4.1–6.9) with an absolute excess risk of 208 cases per 10,000 person-years, whereas the incidence of coronary artery disease matched the general population.[7,8] Because half of the patients died of aggressive NHL prior to living long enough to experience a second cancer, the risk of secondary malignancies was limited to patients treated before the age of 45 years and with an SIR of 3.6 (95% CI 2.0–6.0) and 16.7 (95% CI 1.4–93) for solid tumors and leukemia, respectively.[9] Data on other toxicities showed that infertility (15-year cumulative incidence rate 29%), renal insufficiency (11%), acquired hypertension (8%), and disabling neuropathy (13%) were also frequent. Salvage treatment improved the risk in most cases.[7]

An important ongoing study focuses on the re-habilitation and quality of long-term survival in all 6658 HL patients treated in EORTC trials beginning with the H1 trial. In a tremendous effort, all 3603 surviving patients whose address could be found have been sent an extensive lifestyle questionnaire together with questionnaires related to co-morbidity and chronic fatigue, since more than 60% of survivors complain of persistent fatigue.[28] Over 2000 questionnaires have been returned and are being analyzed. So far, the impact of treatment regimens on premature ovarian failure (POF) occurrence and motherhood has been studied. Non-alkylating chemotherapy appeared to carry little to no excess risk of POF. Linear dose–response relationships could be established for POF with both alkylating chemotherapy and age at treatment.[29] We also investigated the impact of HL on parenthood by comparing survivors with matched general population controls (UNECE Generations and Gender Survey) available for France and The Netherlands. HL survivors had slightly but significantly fewer children after treatment than general population controls. The difference only concerned patients who had children before treatment. However, in patients who attempted post-treatment parenthood, three-quarters succeeded.[30] Simultaneous with this effort, case record forms are being sent to all participating centers to collect detailed clinical follow-up data focusing on treatment-related toxicity. Finally, in-depth studies focusing on pharmacogenetics and psychology will be launched to address the very serious problem of chronic fatigue in HL survivors.

In conclusion, early on investigators were aware of treatment-related side effects, and major attention has been given to following-up on these survivors. Careful prospective collection of detailed data is the basis of clinical epidemiology studies with the objective of assessing the long-term risk of treatment-related complications, rehabilitation and quality-of-life of survivors, and to adapt the treatment strategy to disease aggressiveness.

2.4. Advanced stages

The use of IFRT after chemotherapy for advanced HL is controversial. The LG conducted a trial (H34) in which patients with previously untreated stage III or IV HL in complete remission (CR) after 6–8 cycles of MOPP-ABV were randomly assigned to receive either no further treatment or IFRT. Patients in partial remission (PR) were given IFRT. The results demonstrated that in patients with CR after MOPP-ABV chemotherapy IFRT did not significantly improve the outcome (8-year overall survival rate 82%) and that outcome was not influenced by violation of the radiotherapy protocol. [31,32] Radiotherapy, however, may provide benefit to patients with a PR after chemotherapy (8-year overall survival rate 84%). [33] Subsequently, an intergroup phase III trial (EORTC 20012, 550 patients) comparing BEACOPP *versus* ABVD in high-risk HL patients has recently been closed, and final analysis is expected later this year.

2.5. Relapsed Hodgkin Lymphoma

High-dose chemotherapy (HDCT) followed by autologous stem-cell transplantation (PBSCT) has become the standard treatment for patients with relapsed HL. In these patients, the intensity of treatment has been studied in an intergroup trial. The trial demonstrated that compared to standard BEAM chemotherapy alone, HDCT was associated with more adverse effects and did not improve the prognosis. [34]

2.6. Non-Hodgkin Lymphoma (NHL)

Although the LG has gained experience in the treatment of NHL, the annual patient accrual has been too limited to conduct trials within an acceptable time. Consequently, a decision was made in 2004 to focus on HL, and so the results of NHL studies will not be discussed further in this paper. Recent trials that have been conducted, in part in cooperation with other groups, have concerned: primary CNS-NHL patients treated by MBVP and radiotherapy [35]; newly diagnosed patients with stage III and IV low-grade NHL treated by fludarabine compared to CVP [36]; relapsed/resistant follicular NHL patients given rituximab maintenance to improve clinical results in patients with or without rituximab during induction [37]; the progressive and cautious treatment emphasizing geriatric assessment in diffuse large B-cell and peripheral T-cell NHL in the frail elderly [38]; the prognostic impact of specific treatment protocols on the tumor microenvironment in follicular lymphoma [39]; and the comparison of gemcitabine–(R)CHOP *versus* (R)CHOP in untreated aggressive NHL. In this study, gemcitabine did not improve the results. [40]

3. Conclusion

Hodgkin Lymphoma is a text book example of success in anti-neoplastic treatment thanks to the strategy that has been followed over the last 50 years. The LG has played a major role in this story together with the GELA since the early 1990s and more recently with the FIL. Twenty years ago, the LG took the leadership in this field of clinical research and served as a good example for other European cooperative groups such as the GHSG and the British National Lymphoma Investigation. With the development of more complex studies, i.e., studies including topics in clinical, biological, and social sciences, the LG will continue to participate in trials exploring new treatment strategies and taking into consideration that decision making in cancer treatment should involve patients as much as possible for the benefit of all parties.

4. Future strategy of the group

Current studies concern the long-term outcome and involve HL survivors of the 1964–2004 trials. Another recently approved study is the retrospective analysis of updated data pooled from studies completed by the LG and other cooperative groups worldwide. Upcoming studies are planned for patients with relapsed HL and in elderly HL patients. Translational research (TR) studies will focus on PET imaging and biomarkers. The LG has accumulated expertise in integrating imaging into the treatment sequence and is building on this expertise in the upcoming H11 study on advanced-stage HL. The imaging platform will be used to look for early signs of activity of new targeted drugs. Collaborations with national groups for studies in relapsing HL patients will be continued. Biomarker studies will be done based on old material, and TR projects and biobanking efforts will be expanded to include paraffin-embedded, frozen material and blood (from H10 and H11 studies) to check for markers of late toxicity (e.g. cardiotoxicity). The GELA and the LG are developing the H12 trial, the successor to the H10 study in limited-stage HL together with the FIL.

5. Acknowledgements

This review is dedicated to Prof. Maurice Tubiana, a founder of the EORTC and of the EORTC Lymphoma Group, and his early co-workers who initiated the Hodgkin Lymphoma story, an adventure we are proud to continue.

6. Conflict of interest statement

P. Meijnders, P. Carde, T. Girinsky, J.M.M. Raemaekers, M. Karrasch, M. Henry-Amar, and R. van der Maazen declare no conflicts of interest. J.C. Kluin-Nelemans consulted (non-paid) for Novartis.

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