RECENT APPROACHES IN THE TREATMENT OF HODGKIN'S LYMPHOMA

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An aim has been to find the optimal therapeutic approach for each patient suffering from Hodgkin s lymphoma. The disease with 80% curability rate presents the great success of clinical oncology. There is no doubt that the development and improvement of therapeutic approaches described in this article has contributed to the excellent results achieved in the last twenty years. But a lot of problems still remain to be solved by haemato-oncologists despite such progress in the treatment. The most important tasks are: 1. to increase the curability of advanced stages, 2. to improve therapeutic results in refractory and relapsing patients, 3. to eliminate or decrease the late toxicity particularly in the favourable early and intermediate stages.

INTRODUCTION

Hodgkin's lymphoma with its biological behaviour belongs to non-homogenous malignancies and the origin of tumor elements was the cause of controversy for many years. Nevertheless, this lymphoproliferative disorder (now it is known that tumor cells are derived from B-lymphocytes) represents one of the most therapeutic success in the field of clinical oncology. The curability rate is about 80%!

Some problems still remain in the management of Hodgkin's disease treatment – late therapeutic toxicity in the patients with otherwise favourable prognostic factors associated with high curability rate and the problem of advanced disease, refractory to the therapy or relapsing early after the achievement of complete response. About 50% of the patients with advanced disease either do not achieve complete remission (CR) or relapse early after therapy and many clinical trials have been particularly designed for these patients.

MANAGEMENT OF THE EARLY AND INTERMEDIATE STAGES OF DISEASE

The early and intermediate stages of Hodgkin's lymphoma have been mostly treated with radiotherapy, chemotherapy or the combination of both modalities. There has been very high curability rate in those patients explainable by initially low tumor burden. The treatment of these cases still successfully uses therapeutic approaches designed in sixties or seventies regardless if it concerns radiotherapy (Kaplan, Rosenberg)[26] or chemotherapy (De Vita – MOPP regimen, Bonadonna – ABVD regimen)[6,2].

In the recent years there is an effort to eliminate the risk of late therapeutic toxicity decreasing considerably the quality of life (following infertility of young childless patients, cardiotoxicity, endocrinopathy, secondary cancers, etc.). Secondary malignancies have become a serious problem of the patients who were treated for Hodgkin s lymphoma in childhood or early youth. An incidence of secondary tumors progressively increases in the decades following the treatment[22]. Tumors may be represented by haematological malignancies (acute myeloid leukemias, myelodysplastic syndromes, non-hodgkin's lymphomas) and solid tumors. The development of haematological malignancies is often associated with the previous administration of alkylating cytotoxic drugs sometimes combined with radiotherapy[33,34,35]. Solid tumors usually appear later than haematological cancers and often on the sites irradiated due to initial lymphoma involvement (lung and thyroid gland cancers). Secondary malignancies have become serious treatment complications in the patients with favourable prognosis and high curability rate. They level out originally good therapeutic outcome. Therefore a careful consideration of therapeutic approach with regard to the stage of disease and prognostic features is required.

Hodgkin s disease is divided into 5 subtypes according to the R.E.A.L. classification[15]. The subtypes often differ from each other by various biological behaviour. The lymphocyte predominance Hodgkin s disease (LPHD) subtype often resembles an indolent lymphoma and the patients are usually diagnosed in early stage of disease. Hansmann et al. observed long-term survival in untreated patients with LPHD[14]. The late toxicity has usually represented more important risk than tumor progression. The patients with classical Hodgkin's disease (nodular sclerosis – NS, mixed cellularity – MC, lymphocyte

depletion – LD and lymphocyte rich classical Hodgkin's disease – LRCHD) in early or intermediate stage have been usually treated with radiotherapy or chemotherapy. The advantages of usage both modalities in the combination were assessed in several trials. Such approach prolonged disease free survival (DFS) but without any significant improvement of overall survival (OS) in comparison with one modality (radiotherapy or chemotherapy) treatment[31].

So, what kind of treatment to choose for early stages – "local" radiotherapy or "systemic" chemotherapy? Clinical stages I and II (according to Ann Arbor classification) usually underwent pathological staging in many centres. Pathological staging consists in probatory laparotomy with splenectomy, abdominal lymph nodes and liver biopsy provided despite of normal macroscopic finding. About 30% of patients in clinical stage I or II were reclassified to the stage III or IV according to the pathological staging and required chemotherapy in the first-line treatment. However, there was no significant difference in survival between clinically and pathologically staged patients but a shift to higher incidence of late toxicity was observed in laparotomed and splenectomized patients[23,3]. A deviation from the "classical" strategy with pathological staging has been noted in the recent years. The stratification of the patients according to the early, intermediate and advanced stage of disease which has been designed at the Cotswolds meeting[20] and performed by German Hodgkin's Lymphoma Study Group (GHSG) takes account of some clinical and laboratory characteristics making able to estimate the tumor burden and its activity without laparotomy[3,28] and to choose an optimal therapy.

If radiotherapy has been chosen as only therapeutic modality for the patient with early disease it should be administered by the way of extended field (EF) irradiation (primary involved and anatomically or functionally associated lymph nodes which might be involved despite their normal size). Involved field (IF) irradiation (only involved lymph nodes) should not be used in the treatment without another therapeutic modality because the risk of relapse in the associated lymph nodes would be very high[10]. This kind of radiotherapy should be reserved as an adjuvant therapy to eliminate a residual disease after chemotherapy[7].

The most established chemotherapeutic regimens in the early and intermediate stages of Hodgkin's disease contain following combination of cytotoxic drugs – mustargen or cyklophosphamide, vincristin, procarbazin, prednison (regimen M(C)OPP)[6] and doxorubicin, bleomycin, vinblastin, dacarbazin (regimen ABVD)[2]. Because these two regimens differ principally from each other, the cross-resistance of tumor cells to cytotoxic drugs is not usually developed. The other regimen may be used in the treatment of relapse[27]. The usage of mentioned basic combinations in hybrid or alternating regimens have been usually reserved for the treatment of intermediate and advanced stages.

MANAGEMENT OF THE ADVANCED STAGES OF DISEASE

The advanced stages of Hodgkin's lymphoma represent probably the greatest therapeutic problem and therefore an equal attention has been focused to these patients. High tumor burden is characteristic for the advanced disease. The tumor may involve an extralymphatic tissue including the bone marrow. The massive nodal infiltration creates huge packets ("bulky disease") and tumor activity rapidly deteriorates the condition of patient. Chemotherapy is the treatment of choice in such cases. The advanced disease requires an aggressive therapeutic approach. The combination of 7 or 8 cytotoxic drugs is usually administered in hybrid and alternating regimens[5,36] and they still represent the standard therapy in many centres. The fact that almost 50% of patients with diagnosed advanced disease either did not achieve CR or relapsed early after treatment has led the oncologists and haematologists to search for the new effective therapeutic approaches.

A therapeutic intensification seems to be the way how to improve the results of treatment. Growth factors (G-CSF and GM-CSF) and the rapid development of supportive care have made physicians able to eliminate the toxic events of intensified chemotherapy.

But how to distinguish the patients with the high risk of poor response to conventional therapy or early relapse? Some attempts have been provided to design an appropriate prognostic scale for the patients suffering from advanced Hodgkin s lymphoma[22,24], the equivalent of International Prognostic Index (IPI) for intermediate-grade and high-grade nonhodgkin s lymphomas. The most suitable scale seems to be the prognostic index which was made up by Hasenclever et al.[16]. More than 5.000 patients treated in 23 centres in Europe and the United States were analysed. The scale includes 7 significant risk factors: albumin < 40 g/l, haemoglobin $<$ 105 g/l, male gender, age > 45 years, stage IV, leucocytes $> 15x10^9$/l, lymphocytes $< 0{,}6x10^9$/l or $< 8\%$ in leucocytes differential count. The index value 3 or higher is associated with poor prognosis.

An effort to improve the elimination of tumor has led to the intensification of chemotherapy. The decrease of myelotoxicity and shortening the period of severe neutropenia were achieved with the administration of growth factors available in clinical practice for almost ten years. The therapeutic intensification may be achieved by several ways – dose acceleration, dose escalation or the combination of both approaches. A principle of intensification consists in the elimination of tumor regrowth between the courses as much as possible[21].

The protocol Stanford V represents an example of dose acceleration. It contains the same cytotoxic drugs combination as hybrid regimen MOPP/ABV except procarbazin which was substituted by etoposide[37]. The cytotoxic drugs in Stanford V are administered weekly and one cycle is completed in 4 weeks. 3 cycles of Stanford V take 12 weeks in comparison with hybrid

regimen taking 24 weeks. The Stanford V chemotherapy is followed by IF irradiation (36Gy) in the patients who developed "bulky disease" at diagnosis. There are also another advantages of this regimen. Stanford V is less toxic with regard to the fertility (spermatogenesis has been saved in 97% of male patients) and there has not been observed any significant increase of secondary cancers incidence. And the important issue: Stanford V is more effective in the achievement of CR (92%) than the conventional chemotherapeutic regimens and encouraging 3-years DFS was also reported (78%)[18]. Severe and prolonged neutropenia associated with higher risk of infectious complications can be overcome with G-CSF administration.

The European alternative using intensified therapy for the advanced disease has been represented by GHSG[8,9] with more than 200 cooperative centres in Europe. Over the last twenty years GHSG designed and analysed 3 generations of therapeutic protocols for early, intermediate and advanced Hodgkin's lymphoma. More than 5.000 patients have been enrolled, treated and analysed.

A BEACOPP regimen using the combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristin, procarbazin and prednison was designed in two variants – basic and escalated one. The first variant uses dose acceleration (interval between two courses was shortened to 3 instead 4 weeks required in classical hybrid or alternating regimens) and the both approaches – dose acceleration as well as dose escalation (gradual dose escalation of cyclophosphamide, etoposide and doxorubicin during 4 courses) are involved in the second one. The safe administration of escalated BEACOPP requires growth factors (G-CSF) application to avoid severe prolonged neutropenia[9]. The toxicity of BEACOPP (escalated) seems to be higher than observed in Stanford V including the development of secondary malignancies according to the interim analysis[8,9]. 2% of patients on escalated BEACOPP developed secondary myelodysplastic syndrom or acute myeloid leukemia (two of them with t(9; 11) in cytogenetics). The therapeutic results were found to be very encouraging. CR was achieved in 95%, 2-years DFS 89% and OS 96% of patients. A progression of disease on escalated BEACOPP was observed in 2%[8]. The follow-up of patients enrolled in this study is still very short and the assessment of 5-years DFS and OS including the incidence of late toxicity is awaited. But GHSG study definitively confirmed better therapeutic response to BEACOPP regimen in comparison with COPP/ABVD. Basic variant of BEACOPP was associated with lower toxicity than COPP/ABVD (8, 9) therefore that chemotherapy is considered to substitute COPP/ABVD in the treatment of intermediate stages in next GHSG trial.

The radiotherapy usually belongs to adjuvant therapeutic modalities in the treatment of advanced disease and it is applied to eliminate the residual tumor[8,9,18]. The patient should achieve unless partial remission (PR) (at least 50% resolution of tumor mass) with the first-line chemotherapy. The patient who have achieved only minimal or no response with the primary treatment should not be irradiated without the consideration of salvage chemotherapy including the high-dose one. The radiotherapy in these cases usually presents the waste of time, increases the toxicity and decreases the chance to collect the sufficient amount of stem cells for the high-dose chemotherapy followed by their autotransplantation. The irradiation should be reserved for early stages of Hodgkin's lymphoma eventually for the elimination of residual disease.

MANAGEMENT OF REFRACTORY AND RELAPSING DISEASE

The refractory and early-relapsed cases of Hodgkin's lymphoma represent in clinical practice about 20% of all patients. From 5% to 10% of patients have got extremely aggressive and refractory course of disease with impossibility to be controlled by any of known therapeutic approaches. All these patients have been carefully focused by the haematologists and oncologists. They have been enrolled in various trials comparing different salvage regimens and the high-dose chemotherapy with stem cells support[13,19].

The high-dose chemotherapy with stem cells support (so called autologous transplantation of stem cells) has become a common therapeutic approach in the management of relapsed or refractory disease. Generally accepted criteria for stem cells autotransplantation in the Hodgkin's lymphoma are: 1. relapse of disease until 12 months from CR achievement, 2. subsequently relapsing disease, 3. CR has never been achieved with regimens combining 7 or 8 cytotoxic drugs in the first-line therapy. Autologous transplantation has become a routine and standard approach in these cases. Nevertheless, there are another indication possibilities which remain the item of clinical trials. One example could be the high-dose chemotherapy with stem cells rescue performed in CR but in the patients with unfavourable prognostic factors[4]. But whose of such patients is really in the certain risk of relapse? Where does the border between the risk of relapse and transplant related complications lie? The refractory patients represent further group suitable for the high-dose therapy. The disease does not respond or progresses on conventional therapy and the salvage regimens are usually not very successful in such cases. We should estimate the behaviour of disease according to response to the first chemotherapeutic courses with regard to the prognostic factors. Poor responders might be the appropriate candidates for so called tandem autologous transplantation of stem cells[25]. The administration of two myeloablative conditioning regimens following in the short period of time can reverse unfavourable prognosis[1]. But such patients should be recognized and indicated early. Therefore intermediate restaging after the first half of primary chemotherapy seems to be a valuable procedure.

Allogeneic haemopoetic stem cells transplantation has not fully established in the treatment of refractory or relapsing Hodgkin's disease, yet. There have been several reasons. The previous salvage regimens and the high-dose chemotherapy in the refractory and relapsing cases significantly increases the incidence of toxic complications after allogeneic transplantation and the risk of peritransplant morbidity and mortality. But such approaches have been generally chosen as the first option due to their high therapeutic effect in the most of refractory or relapsing patients. We need to distinguish the patients incurable with mentioned procedures. They would become the candidates of allogeneic stem cells transplantation. The allografting represents the most effective form of immunotherapy. Besides conditioning regimen the tumor cells are eliminated by graft-versus-tumor reaction which is realized by the immunocompetent donor cells. However, myeloablative conditioning in this procedure is associated with high toxicity, peritransplant morbidity and mortality mainly in heavily pretreated patients. Only about 20% of such patients belong to the long-term survivors according to the European Group for Blood and Marrow Transplantation (EBMT) data.

New encouraging therapeutic method in this field seems to be nonmyeloablative allogeneic stem cells transplantation which avoids the high toxicity of conditioning regimen and relies on the graft-versus-tumor reaction induced by donor lymhocytes[29]. But such procedures still remains the item of clinical trials and needs probably some time to become the standard treatment of refractory Hodgkin's disease.

An immunotherapy alone does not represent the standard treatment of Hodgkin's lymphoma. The results of some clinical trials with monoclonal antibodies, immunotoxins, IL-2 fusion toxins have rather disappointed oncologists and haematologists so far[11,12,17,32].

CONCLUSION

The patients with refractory and relapsing Hodgkin's lymphoma represent the main therapeutic problem and the most of them have been usually diagnosed in advanced stage of disease. The most important task for physicians is to recognize them and change actually the standard therapeutic strategy in such patients.

Therapeutic modalities should be carefully considered in the patients with early or intermediate stage of disease due to the late toxicity risk which might lead to the severe deterioration of patient's condition or to the death in complete remission of Hodgkin's disease.

Alternative biological therapeutic approaches (immunotherapy, gene therapy, etc.) need further investigation and assessment in the basic research and clinical trials. Now they do not represent the modalities which would enable us to leave the aggressive and toxic but still relatively effective procedures.

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