Symposia

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Results of time and dose intensification in high-grade NHL

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The intergroup study by Fisher et al. (1993) confirmed that CHOP is as effective as more dose-intense regimens of the second and third generation disapproving of the classical concept of dose intensity. A reevaluation of available data derived from randomized trials led to the new concept of effective dose (ED). This concept reveals that CHOP emphasizes drugs with a high individual ED and that the common high-grade NHL regimens used to date including those which employ high-dose chemotherapy with stem cell support have very similar cumulative ED. To optimize cumulative ED, the GHNHLSG started a randomized dose escalation trial to determine the maximal practicable dose (MPD) for CHOEP given either every 2 or every three weeks (hi-CHOEP-14 vs. hi-CHOEP-21) with G-CSF. To date 56 patients have been included and the following dose-escalations were feasible: hi-CHOP-14: Doxo +20%, Cyclo +60%, Eto +50; CHOEP-21: Doxo +40%, Cyclo +133%, Eto +100. This demonstrates that the "intelligent" use and escalation of drugs with high individual ED for high-grade NHL permits the appplication of polychemotherapy regimens with total ED levels comparable to or superior to the total ED of regimens which require stem cell support, but without the toxicity and the costs of the latter. Randomized phase-III trials of the GHNHLSG are ongoing which will prove or disapprove the validity of the concept of ED in a prospective manner.

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New trends in Hodgkin's disease

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Hodgkin's disease represents a clonal B-cell lymphoma in most if not all cases. At present over 90% of patients with early stage Hodgkin's disease are cured. Both radiotherapy and combination chemotherapy are effective treatment modalities. However, the optimal choice of treatment or combinations of treatment is still debated. Recently, several trials reported excellent treatment results with combined modality in early stages of Hodgkin's disease. The use of chemotherapy regimen not including alkylating agents may avoid the risk of infertility and secondary malignancies and facilities reduction of dose and field size of radiotherapy in early stages. In intermediate stages new chemotherapy regimen (i.e. BEACOPP) will offer the chance to reduce the fraction of patients with initial treatment failure, while reducing the extent of radiotherapy. With the introduction of the escalated BEACOPP regimen it was demonstrated that the prognosis of the advanced stages could be positively influenced by intensification of therapy. Future trials aim to answer 1) which chemotherapy regimen in which quantity will be the best with respect to efficacy and long-term toxicity and 2) which dose and field size of radiotherapy is adequate within the combined modality approach.

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Abstract not received.

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New treatment approaches to lymphoma with monoclonal antibodies

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Because of the diversity of non-Hodgkin's lymphomas, their treatment is quite impossible to summarize event if some standards become available in some entities or some clinical situations. Thus, when a new therapeutic agent is introduced, finding its place in the different therapeutic possibilities needs time. MabThera, an anti-CD20 chimeric monoclonal antibody, has efficacy in CD20-positive B-cell lymphomas and it has considerably increased the therapeutic combinations used in these patients. A summary of the current indications and of the investigated indications of this novel agent will be presented. The place of MabThera will be defined along with the different monoclonal antibody agents, immunotoxins, radio-labeled antibodies with 131I or 90Y. Activity, limitations, and potential problems will be reviewed.

The first indication of MabThera was relapsing follicular or indolent lymphoma and all data concerning these results will be reviewed. The usefulness of MabThera in these relapsing patients will be summarized. Future aspects of MabThera in this group of patients will be presented. Ongoing trials in association with chemotherapy or in first line patients will be discussed. MabThera may have activity in other CD20+ B-cell lymphomas and the first trials in diffuse large cell lymphoma or mantle cell lymphoma confirm its efficacy, even if it is lower in relapsing aggressive patients than in relapsing indolent patients. Here too, the ongoing trials studying the efficacy and safety of the combination of MabThera plus chemotherapy will be presented. The potential efficacy of MabThera in others B-cell cancers, such as marginal zone lymphoma, chronic lymphocytic leukemia, or myeloma, will be discussed. The place of MabThera in special indications will be discussed. Maintenance therapy in responding patients is just beginning to be tested but the concept of in vivo purge before harvesting stem cells for autotransplant is more advance and preliminary results are encouraging. Technical problems such as the dose, the number of infusions, the combination with chemotherapy agents will be discussed.

Safety and most frequently observed adverse events in these different situations will be presented as well as their mechanism. Current prevention of these events will be summarized.

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Immunotherapy of lymphoma by cytokines and allogeneic cell therapy

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Rational therapeutic options for resistant lymphoma patients include autologous stem cell transplantation (AST). We have shown in mice and man that at the stage of minimal residual disease (MRD), lymphoma may be controlled by α-interferon and rIL-2. A phase III study is underway to confirm the preliminary study. For patients with a matched sibling or matched unrelated donor (MUD), allogeneic bone marrow transplantation (alloBMT) may represent the treatment of choice due to the added benefit of graft versus lymphoma (GVL) effects mediated by alloreactive donor lymphocytes. Until recently, myeloablative conditioning with a combination of chemotherapy or chemoradiotherapy at maximally tolerated doses to eradicate all malignant cells was considered mandatory. Unfortunately, alloBMT is associated with procedure-related immediate and long-term toxicity and mortality. Starting in early 1987, we have documented that tumor cells fully resistant to maximal tolerated doses of chemoradiotherapy may still be eradicated by donor lymphocyte infusion (DLI). The cumulative data in experimental animals and man suggested that immunotherapy mediated by alloreactive DL may be the most effective approach to eradicate all hematopoietic cells of host origin, thus suggesting that the benefits of conventional alloBMT might be achieved with better tolerated and less hazardous conditioning involving nonmyeloablative stem cell transplantation (NST). Our working hypothesis lead to the development of a new protocol which consists of inducing a "window" of immunosuppression rather than myeloablative conditioning, as a platform for adoptive allogeneic cell therapy mediated by donor lymphocytes. Using NST, patients with resistant lymphoma, including patients failing AST regardless of their resistance to chemoradiotherapy were effectively treated since GVL effects mediated by DL could mediate remission. Our cumulative clinical experience will be reviewed.