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EXPERT REVIEWS

Hodgkin lymphoma: highlights from the 2012 European School of Hematology International Conference

Expert Rev. Hematol. 6(1), 35–37 (2013)

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ESH International Conference on Lymphomas
Marseille, France, 28–30 October 2012

The ESH International Conference on Lymphomas gathered clinicians and scientists involved in all aspects of clinical treatment and biology of lymphomas. The 2012 International Conference was held in Marseille, France, and presented an appealing program. Of particular interest was the session dedicated to Hodgkin lymphoma. Our knowledge on the pathology of Hodgkin lymphoma and on the new therapeutic possibilities has changed greatly during the last three decades. During the session, the speakers focused on the results of conventional chemotherapy and on the new drugs for resistant/relapsed patients.

Therapeutic advances over the last three decades have resulted in the cure of the majority of Hodgkin lymphoma (HL) patients [1]. Despite the excellent results achieved, several questions remain. In the session of the Conference dedicated to HL, four different aspects were focused on: the role of the microenvironment (Randy Gascoyne, British Columbia Cancer Agency, Vancouver, BC, Canada), the therapy of early- and advanced-stage HL (James Radford, Cancer Research Campaign Department of Medical Oncology, Christie Hospital National Health Service Trust, Manchester, UK and Andreas Engert, University Hospital of Cologne, Department of Internal Medicine I, Köln, Germany), the treatment of recurrence (Anna Sureda, Addenbrookes Hospital, University of Cambridge, Cambridge) and the new drugs for relapsed/refractory patients (Andrew Davies, Cancer Research UK Medical Oncology Unit, St Bartholomew's Hospital, London, UK).

The microenvironment & HL

The Hodgkin and Reed-Sternberg (HRS) cells have two major aims. First is to promote survival and proliferation of themselves and, second, to cultivate immune privilege through a number of immune escape mechanisms. The microenvironment is not an innocent bystander, but an important functional part of the tumor. As already known, the microenvironment in HL is composed of a heterogeneous infiltrate of innate immune cells including neutrophils, eosinophils, mast cells, macrophages, antigen-responsive immune cells including B and T lymphocytes and stromal- or antigen-presenting cells including fibroblasts, fibroblastic reticular cells and follicular dendritic cells. "A key feature of HL biology is the extensive crosstalk between the malignant HRS cells and the non-neoplastic cells in the microenvironment that both sustain the survival of the HRS cells and also fosters immune privilege. The language of this crosstalk includes a number of chemokine and cytokine networks as well as numerous receptor–ligand interactions that require cell–cell contact", said R Gascoyne. The cytokine storm that is the milieu of HL is fundamental to the survival of the HRS cells and largely explains most of the histopathology and biology of this lymphoma. The role of macrophages has been widely discussed, and the new data solidified the role of these cells that can offer an important contribution for survival [2].

 10.1586/EHM.12.73 © 2013 Expert Reviews Ltd ISSN 1747-4086

Therapy of early stage

The treatment for early-stage HL has evolved considerably over the last four decades. The acute and delayed toxicity of alkylating agent-based therapies, in particular infertility and secondary leukemias, led to their replacement with adriamycin-containing regimens (ABVD). Concerns about the solid tumors and cardiovascular disease risks associated with radiotherapy resulted in smaller field sizes and lower doses first being assessed in clinical trial and later introduced into clinical practice. "Now as little as 2 cycles of ABVD followed by 20 Gy of involved field radiotherapy can be recommended in patients with favourable risk, early stage, approach that is the culmination of years of work involving many thousands of patients taking part in clinical trials" said Radford. Current research is focused on evaluating PET imaging as a biomarker of disease elimination. A number of clinical trials in this area is underway and the results of these will inform next steps in our ambition to maximize the chances of cure while minimizing the risks of late toxicity for patients with early-stage HL.

Therapy of advanced-stage HL

ABVD is considered the standard-of-care for advanced HL, providing an excellent balance of efficacy and toxicity. "While ABVD is accepted by all for most early-stage patients, in advanced stages ABVD has been reported to have a poorer prognosis with a reported failure-free survival at 5 years ranging between 63 and 66% in multicenter trials; in contrast, the multi-agent BEACOPP regimen (bleomycin, etoposide, adriamycin [doxorubicin], cyclophosphamide, vincristine [oncovin], procarbazine and prednisone) in its escalated version has given more impressive results with tumor control rates at 5 years of 87% and overall survival rates of 91%" said Engert. Despite these better results, BEACOPP escalated was associated with more hematological toxicity as compared with the baseline version of COPP (cyclophosphamide, vincristine, procarbazine and prednisone)/ABVD and induced more infertility in both male and female patients [3]. In addition, the rate of secondary acute myeloid leukemia was higher with BEACOPP escalated. Importantly, six cycles of BEACOPP escalated were also less toxic as compared with eight cycles [4]. Thus, six cycles of BEACOPP escalated constitute the new standard-of-care in most European countries.

BEACOPP escalated is more toxic in patients over 40 years of age, particularly if they have a poorer performance status (Easter Cooperative Oncology Group 2 or Karnofsky <80%). Engert concluded that "future clinical trials could include one or two initial cycles of BEACOPP escalated which is followed by ABVD (Kairos principle) in PET-negative patients. PET-positive patients continue on BEACOPP escalated. An alternative is to start with ABVD and escalate if there is no sufficient response (Chronos principle)."

Treatment of recurrence

High-dose therapy followed by autologous stem cell transplantation (ASCT) is now considered the standard-of-care for relapsed/resistant HL patients. The impact of ASCT in the long-term outcome of patients with relapsed/refractory HL is not the same in all subgroups of patients. "Time to relapse (<12 months vs ≥12 months), extranodal disease at relapse, advanced stage and anemia at relapse, B symptoms and refractory disease were found to be important" said Sureda. The presence of significant anemia at the time of relapse, early or multiple relapses and stage IV represented a very small group of patients with a dismal overall outcome and a 3-year progression-free survival (PFS) of less than 20%. Recently, the results of fluorodeoxyglucose-PET at the end of salvage CT and before the ASCT have also been analyzed in HL patients.

In the attempt to improve the results of conventional ASCT, the German Hodgkin Study Group developed a sequential high-dose chemotherapy that was used before the transplant conditioning itself. These promising results prompted the German Hodgkin Study Group to develop a prospective Phase III clinical trial. No significant difference in terms of PFS, freedom from treatment failure or overall survival were found between the study arms.

The advent of reduced-intensity conditioning regimens renewed the enthusiasm of the scientific community on the use of allogeneic stem cell transplant (allo-SCT) in relapsed HL [5,6]. "The results of the largest and recently published prospective Phase II clinical trial including 78 patients with a median follow up of 4 years after allo-SCT indicate a NRM of 8% at 100-days and 15% at 1-year. Relapse was the major cause of failure PFS was 48% at 1-year and 24% at 4-years. Chronic graft-versus-host disease was associated with a lower relapse incidence and a better PFS. Patients allografted in complete response (CR) had a significantly better outcome. In this study OS was 71% at 1-year and 43% at 4-years, respectively" said Sureda. Results of donor lymphocyte infusions (DLIs) in patients with HL represent a source of indirect evidence of the existence of a clinically beneficial graft versus lymphoma effect. The most extensive piece of evidence in this sense comes from the UK cooperative group. Forty six consecutive patients with multiple relapsed or refractory HL who underwent allogeneic transplantation that incorporated *in vivo* T-cell depletion received DLIs because of disease relapse or mixed chimerism after allo-SCT. In a T-cell depleted setting, DLIs were able to reduce the relapsed/refractory disease as well as to induce durable antitumor responses. Brentuximab vedotin, a new anti-CD30 monoclonal antibody, is highly effective in the treatment of relapsed HL. The recent paper by Chen *et al.* confirmed the efficacy of the combination of brentuximab vedotin followed by reduced intensity conditioning [7].

In conclusion, ASCT remains the standard-of-care for most chemosensitive relapse HL patients. Allo-SCT should be confirmed the most frequently used treatment strategy in ASCT failures if the patient is young, has chemosensitive disease and an appropriate donor available.

New drugs for HL

Davies discussed what can be done in healthy patients who relapse after ASCT and/or allo-SCT. Bendamustine has demonstrated good responses in these patients: 38% of patients achieved a CR.

Panobinostat, an orally active pan-deacetylase inhibitor, demonstrated an overall response rate (ORR) of 27% in a study of 129 patients primary refractory or relapsed within 12 months of high-dose therapy. The median duration of response was 7 months, with the major toxicity being thrombocytopenia. Everolimus, an oral active inhibitor of the mTOR pathway, demonstrated an ORR of 47% in a population of 17 patients who had received a median of six prior therapies.

The interaction between the HRS cell and the infiltrating microenvironment is critical in the propagation of HL. Lenalidomide has multiple mechanisms of actions including modulation of the microenvironment and direct antilymphoma effects. In a study of 38 patients, of which 87% had had prior high-dose therapy, the ORR was 19%, with 3% reaching a CR. A third of patients experienced disease stabilization on therapy.

The CD30 antigen is highly expressed on HRS cells. Brentuximab vedotin is an antibody-drug conjugate targeted at CD30, delivering the anti-tubulin agent auristatin (MMAE) intracellularly. In the pivotal Phase II study, given every 3 weeks, the ORR of 102 patients was 75% with 34% of patients achieving a CR [8]. Response durations are impressive. The main toxicity has been peripheral sensory neuropathy.

Other agents are in clinical development, and all these agents hold promise. The future direction will come from combination studies with these agents and conventional therapies.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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