Are macrophages the bad guys in Hodgkin lymphoma?

Volker Diehl

Prognostic models for patients with Hodgkin lymphoma are imperfect and do not allow a precise individualised therapy. A recent gene-expression profiling study, translated into a routine immunohistological test, identified genes of tumour-associated macrophages as being responsible for treatment outcome in patients with Hodgkin lymphoma. If this finding is confirmed by other investigators, it could be a major step towards personalised therapy for patients with Hodgkin lymphoma.

Patients with Hodgkin lymphoma (HL) with early-stage disease are cured in >95% of cases, and in patients with intermediate-stage and advanced-stage disease, cure rates of 80%–90% are achieved with modern treatment strategies consisting mainly of polychemotherapy with or without radiotherapy. In the future, these treatments might be complemented by therapies based on small molecules and antibodies.[1] This unusual success rate in the treatment of an adulthood cancer, however, is associated with an inevitable burden of overtreatment and undertreatment of at least 10%–20% of patients in all stages of disease, which can result in unnecessary early progression or late toxic effects. Since the pathognomonic Reed–Sternberg cells (0.1%–1.0% at diagnosis) and the surrounding so-called 'innocent bystander cells'[2] are very sensitive to chemotherapy and radiotherapy, more than 90% of patients with HL experience a first complete remission at onset. However, 20%–30% of the tumours will progress or relapse. These failures cannot be predicted with certainty using available clinical, biological or molecular biomarkers.

Currently, there are two strategies that aim to tailor therapy at diagnosis on the basis of response and outcome prediction for the individual patient, which are not robust measurements. The first is risk adaptation, in which the clinical and biological International Prognostic Score is used for advanced-stage

nature REVIEWS CLINICAL ONCOLOGY

This article was first published in *Nature Reviews Clinical Oncology* 2010 vol.7 no.6, and is published with permission. doi:10.1038/nrclinonc.2010.71, www.nature.com/nrclinonc

disease,[3] or the Ann Arbor classification and tumour burden that is used in early-stage disease. The second strategy is response modulation, in which therapy is escalated or reduced according to the FDG PET/CT result after two courses of induction therapy.[4] Both strategies are applied in ongoing international HL trials, yet they are far from offering the necessary accuracy to provide a personalised treatment option for individual patients.

The recent study by Steidl et al.,[5] however, opens a new hopeful avenue to reach the goal of personalised medicine. In this publication, the authors describe a method for predicting HL outcome by applying a frequently used but often-underestimated pathology test.

The researchers (a combination of pathologists, molecular biologists, biostatisticians and clinicians) measured the amount of CD68+ macrophages in the primary tumour lesions of patients with HL and correlated the percentage of CD68+ macrophages (immunohistochemical score 0–3) to the outcome of therapy.

This association was relevant for the induction treatment phase. Furthermore, the quantity of CD68+ tumour-associated macrophages predicted success or failure in the setting of disease-relapse after autologous haematopoietic stem-cell transplantation.

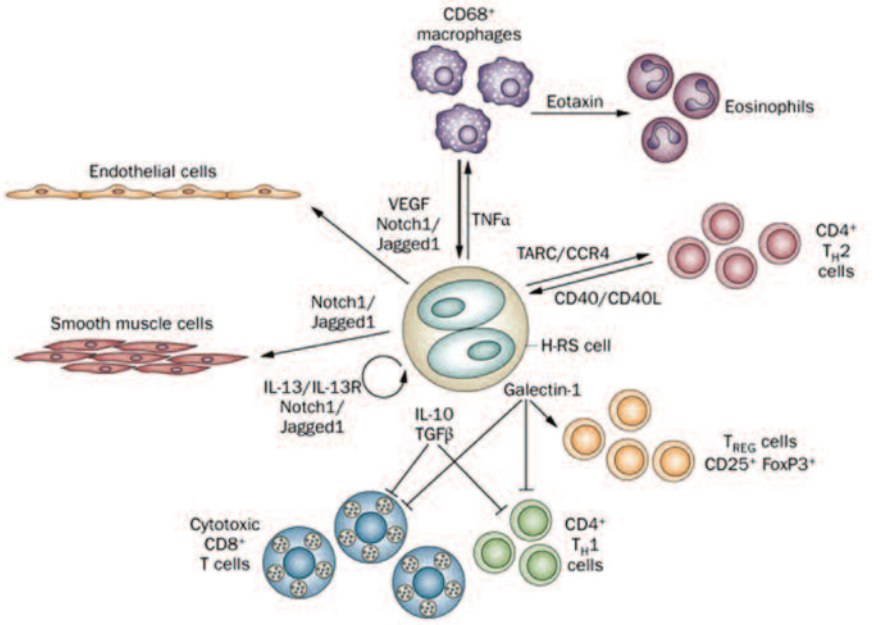
Gene-expression profiling studies on a set of 130 frozen biopsy samples revealed a group of genes that showed a significant correlation between the gene-expression profile and the outcome of primary and secondary treatment. The validity of these findings was confirmed in an independent cohort of 166 patients with classic HL, using immunohistochemical analysis of tumour tissue on paraffin blocks.

These findings, along with previous studies,[6,7] revealed three major factors that correlate with the failure of primary HL therapy: the abundance of tumour-infiltrating macrophages, the lack of small B-lymphocytes, and the overexpression of metallopeptidases (such as MMP11).

Steidl et al.[5] focused on the CD68+ macrophages because of the strong signals from the gene-expression data and the prominent role of macrophages in the process whereby tumour cells interact with bystander cells, such as macrophages, eosinophils, mast cells, B-cells and T-cells (see figure). These interactions lead to an inhibition of apoptosis, which increases proliferation and promotes the survival of tumour cells, not only in HL but also in follicular non-HL,[8] as well as in other B-cell malignancies.[9]

The immunohistochemical macro-

INTERACTION OF H-RS CELLS WITH THE MICROENVIRONMENT



The interactions between H-RS cells and the microenvironment include mediators and reactive innate immunity bystander cells. CD68+ macrophages are activated by TNFα and the fragile H-RS cells are regulated by mediators such as Notch1/Jagged1, and by the angiogenic switch, which is controlled by VEGF in conjunction with endothelial and smooth muscle cells. H-RS cells attract CD4+ lymphocytes via TARC/CCR4 and interact with the CD4- cells via CD40–ligand interaction. Cytotoxic CD8+ T-cells and CD4+T_H1 cells are kept at a distance from the H-RS cells and inhibited by IL-10, TGFβ and galectin-1, which in turn activates CD25+ FoxP3+ T_{REG} cells. A paracrine loop via IL-13/IL-13R assisted by Notch1/Jagged1 promotes proliferation of H-RS cells.

CCR4 – chemokine receptor 4; H-RS – Hodgkin-Reed–Sternberg; IL-10 – interleukin-10; TARC – thymus and activation-regulated chemokine; TGFβ – transforming growth factor-beta; TNFα – tumour necrosis factor-alpha; T_{REG} cells – T-regulatory cells; VEGF – vascular endothelial growth factor

phage score in the primary tumour lesion of patients with HL not only predicted the outcome in advanced stages of the disease but, furthermore, indicated a 100% chance of long-term, disease-specific survival in the absence of an increased number of CD68+ cells. Moreover, in advanced stages of classic HL, this molecular adverse prognostic factor significantly outperformed the International Prognostic Score for disease-specific survival (P=0.003 vs P=0.03, respectively).

The important question is whether these findings will have a notable impact on general practice in the management of HL patients?

As DeVita and Costa[10] point out, it is of pivotal importance that a personalised treatment strategy is developed in the future treatment of patients with HL, to identify at diagnosis those individuals with increased resistance to chemotherapy and radiotherapy, thus enabling clinicians to adjust the quality and quantity of drug combinations for individual patients.

This pioneering study, however, was a retrospective analysis, and confirmation of the results by other investigators is needed to ascertain the validity of these findings in a large number of patients and in a prospective setting – especially when treating patients with advanced-stage disease with a more aggressive regimen, such as escalated-dose BEACOPP.

An additional future requirement will be to translate this diagnostic method into a treatment strategy to allow a prognostic allocation of patients. Further studies will also need to consider whether the determination of the number of CD68+ macrophages in the tumour lesion of a patient with HL will be sufficient to predict outcome, or whether an accurate prediction will also depend on measurement of the B-cell content and the MMP11 metallopeptidase activity.

It seems likely that this information could gain widespread use, since the determination of CD68+ tumour-associated macrophages by immunohistology is already a routine test for diagnosis of classic HL in most experienced haematopathology institutions. Furthermore, since the necessary techniques are already established in most laboratories, it is cost-effective and reproducible.

Many pathologists have described CD68+ macrophages in the biopsies of patients with classic HL, and many clinicians in recent years have read this information in their pathology reports. Why then was this association not recognised earlier and used to predict outcome as a simple, frequently used test?

Possibly, the simple answer is that clinicians and pathologists did not put the pieces of this molecular-biological puzzle together as Steidl et al.[5] have now done. Indeed, this study is an excellent example of interdisciplinary collaboration, often referred to as 'translational research' or 'patient-oriented research', which reaches from the bench to the bedside!

Practice point

In a recent study, a frequently used immunohistologic diagnostic test was used to measure the amount of CD68+ macrophages in the primary tumour lesions of patients with Hodgkin lymphoma. This macrophage score not only predicted outcome of therapy in disseminated stages, outperforming the International Prognostic Score (IPS), but also predicted outcome in localised stages and indicated a 100% chance of long-term disease-specific survival when the score was low.

References

1. M Fuchs, V Diehl and D Re (2006) Current strategies and new approaches in the treatment of Hodgkin's lymphoma. *Pathobiology* 73:126–140

2. R Küppers. (2009) The biology of Hodgkin's lymphoma. *Nat Rev Cancer* 9:15–27

3. D Hasenclever and V Diehl. (1998) A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on advanced Hodgkin's disease. *NEJM* 339:1506–1514

4. M Hutchings et al. (2006) FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood* 107:52–59

5. C Steidl et al. (2010) Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. *NEJM* 362:875–885

6. A Sánchez-Aguilera et al. (2006) Tumor microenvironment and mitotic checkpoint are key factors in the outcome of classic Hodgkin lymphoma. *Blood* 108:662–668

7. E Devilard et al. (2002) Gene expression profiling defines molecular subtypes of classical Hodgkin's disease. *Oncogene* 21:3095–3102

8. SS Dave et al. (2004) Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *NEJM* 351:2159–2169

9. JA Burger, P Ghia, A Rosenwald et al. (2009) The microenvironment in mature B-cell malignancies: a target for new treatment strategies. *Blood* 114:3367–3375

10. VT DeVita Jr and J Costa. (2010) Toward a personalized treatment of Hodgkin's disease. *NEJM* 362:942–943

Author affiliations: Department of Internal Medicine, Haematology-Oncology, University of Cologne, Germany
Competing interests statement: The author declares he is a consultant for Seattle Genetics