Mini Review

Disease-specific biomarkers for early diagnosis of hematologic malignancies

Abstract

Cancer diseases are intractable disorders, involving pathological activities mediating tissue destruction. In Europe, and other parts of the world, these diseases cause immense human suffering and inflict on society an annual economic burden of hundreds of billions of Euros, associated with direct and indirect medical costs resulting from lost work time, disability payments and premature death. Traditional treatments and drugs for various cancer diseases either produce undesirable side effects or provide a relief of symptoms or delay in deterioration rather than a cure. Most, if not all, have the deleterious effect of destroying normal cells as well as the cells involved in pathological activities. Results of efforts made to develop improved treatments for cancer diseases using disease specific cell surface chemical entities have been disappointing until now. In this mini-review we are reporting about a novel diagnostic kit for the measurement of disease-specific forms of galectin and CD44 proteins in different haematological malignancies (HM).

Keywords: haematological malignancies, CD44, HM, disease, symptoms

Itshak Golan
Daniel & Daisy Novel Therapeutics Ltd., United Kingdom

Correspondence: Itshak Golan, Daniel & Daisy Novel Therapeutics Ltd., 49 Southern down Avenue, Mayals, Swansea SA3 5EL, United Kingdom, Tel 44-1792-404-122, +44-77-9123-5930, Email i.golan@swansea.ac.uk

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Introduction

Prior to diagnosis, patients with haematological cancers often have multiple primary care consultations, resulting in Diagnostic Delay. They are less likely to be referred urgently to hospital and often present as emergencies. Howell et al.[1] examined patient perspectives of time to help-seeking and diagnosis, as well as associated symptoms and experiences using the following method; The UK's Haematological Malignancy Research Network (www.hmrn.org) routinely collects data on all patients newly diagnosed with myeloma, lymphoma and leukaemia (>2000 annually; population 3.6 million). With clinical agreement, patients are also invited to participate in an on-going survey about the circumstances leading to their diagnosis (presence/absence of symptoms; type of symptom(s) and date(s) of onset; date medical advice first sought (help-seeking); summary of important experiences in the time before diagnosis). From 2004-2011, 8858 patients were approached and 5038 agreed they could be contacted for research purposes; 3329 requested and returned a completed questionnaire.

The duration of the total interval (symptom onset to diagnosis), patient interval (symptom onset to help-seeking) and diagnostic interval (help-seeking to diagnosis) was examined by patient characteristics and diagnosis. Type and frequency of symptoms were examined collectively, by diagnosis and compared to UK Referral Guidelines.

The results of this investigation were: Around one-third of patients were asymptomatic at diagnosis. In those with symptoms, the median patient interval tended to be shorter than the diagnostic interval across most diseases. Intervals varied markedly by diagnosis: acute myeloid leukaemia being 41 days (Interquartile range (IQR) 17-85), diffuse large B-cell lymphoma 98 days (IQR 53-192) and myeloma 163 days (IQR 84-306). Many symptoms corresponded to those cited in UK Referral Guidelines, but some were rarely reported (e.g. pain on drinking alcohol). By contrast others, absent from the guidance, were more frequent (e.g. stomach and bowel problems). Symptoms such as tiredness and pain were common across all diseases, although some specificity was evident by sub-type, such as lymphadenopathy in lymphoma and bleeding and bruising in acute leukaemia.

The conclusions of this study are: Pathways to diagnosis are varied and can be unacceptably prolonged, particularly for myeloma and some lymphomas. More evidence is needed, along with interventions to reduce time-to-diagnosis, such as public education campaigns and GP decision-making aids, as well as refinement of existing Referral Guidelines.[1]

It is clear that there is a current unmet medical need for a novel diagnostic kit which will diagnose more accurately and earlier, the presence of haematological malignancies. In our recent studies, we discovered genetically modified variants of two biomarkers, expressed during early stages of the establishment of the tumorigenic conditions; galectin-9 (one isoform) and CD44 proteins (two isoforms). These proteins designated by us as HM-specific galectin-9 and HM-specific CD44 variant-1 and variant-2. These proteins were not identified in other clinical samples from different cancers that tested by us.

We are planning to utilize these discoveries to develop and commercialise robust diagnostic and prognostic assays that will guide treatment choices and leading to improved patient care for HM patients. The clinical and business advantages, of the new developed diagnostic kit, are huge, and will be demonstrated during the project that we are planning during next months, by testing the performance, of the kit prototype, using clinical samples from human patients with different haematological malignancies.

The social problem to overcome and the resulting business opportunity; cancer-hematologic malignancies

Hematologic malignancies represent the fifth most commonly occurring cancers and the second leading cause of cancer death. Tumours of the hematopoietic and lymphoid malignancies affect the blood, bone marrow, lymph, and lymphatic system.[2,3] As those elements are all intimately connected through both the circulatory system and the immune system, a disease affecting one will often affect the others as well, making myeloproliferation and lymphoproliferation (and thus the leukemias and the lymphomas) closely related and often overlapping conditions. The diagnosis of the hematologic cancers presents a daunting challenge. At every stage

of normal hematopoietic differentiation a number of biologically and clinically distinct malignancies may arise. Inherited DNA-sequence variants do not appear to have a prominent causative role; rather, these diverse cancers are typically initiated by acquired alterations to the genome of the cancer cell, such as chromosomal translocations, mutations, and deletions. The diagnosis of the hematologic cancers is commonly based on morphologic evaluation supplemented by analysis of a few molecular markers. However, in some diagnostic categories defined in this fashion, the response of patients to treatment is markedly heterogeneous, arousing the suspicion that there can be several molecularly distinct diseases within the same morphologic category.[4]

A direct leukemic or tumour cells analysis is the only certain way to diagnose different types of hematologic malignanices, such as lymphoma, leukemia, and multiple myeloma, while a blood test and cytogenetic analyses can help diagnose different subtypes of these conditions.[5-7] Treatment options for the patients depend on the specific type of tumour, stage of the disease, the speed at which the cancer is growing, and the patient's overall health. Based on these factors, treatment may include chemotherapy, targeted therapies, biologic therapy and blood stem cell transplant.[8] Hence, it is important to develop robust and sensitive early diagnostic tool for different hematologic cancer conditions, in order to enable appropriate and effective treatments for the patients.

Novel HM-specific biomarkers for early diagnosis of different hematologic malignancy conditions

In recent years, we completed screening study of clinical samples from different haematology malignances and found two diseases-specific CD44 variants (CD44vH1 and CD44vH2) expressed in myeloma and lymphoma patients. More recently, we identified modified human galectin-9 molecule in clinical samples of bone marrow and PBLs derived from 141 human patients with different hematological malignances. This disease-specific variant designated as hematology-specific human galectin-9 protein. We are planning utilize the discovery of disease-specific CD44/galectin proteins, in hematologic malignancy conditions, to develop a novel innovative diagnostic kit for early diagnosis of these conditions that will be used in the clinic also for optimal choice of the treatment methods.

An important spin-off from this research will be to use these biomarkers for therapeutic indications. This is based on the proven ability of the galectin proteins and anti-CD44 mAbs to induce apoptosis in-vitro/ex-vivo in pathological inflammatory and cancer cells from human patients.[9-12]

The novelty of this innovative business project

The main advantage, for market success, of the innovative technologies developed by us and presented here is its' potential to provide novel biological drugs with improved safety and efficacy. Our therapeutic program will follow the diagnostic tool development which is the first step for establishment of highly innovative and promising technologies using novel biomarkers for therapy and diagnosis of different hematologic malignancy conditions. In our future therapeutic programs, we will offer specific and selective targeting of the cancer cells (which express the HM-specific biomarkers) involved in the pathological activities of these diseases. We will target the cancer cells directly while leaving the normal tissues/organs unaffected. Our technology, if success, have a potential to provide specific and safer therapies for these diseases.

The technology involved in development of galectin/CD44 molecules for diagnostic, prognostic and therapeutic indications for HM has many advantages

For the diagnostic/prognostic indications

a. The novel sequences of HM-specific galectin/CD44 proteins are highly patentable and will not break any existing IP rights of other organizations. We covered, by patents, HM-specific human-galectin-9 variant and HM-specific CD44 sequences and have full FTO to utilize this technology for our commercial purposes.

b. Early diagnosis; the galectin/CD44 proteins are expressed in early stages during the establishment of the pathological conditions in different hematologic malignancies and have huge potential in the clinic for early diagnosis of these conditions that will lead to optimal choice of the treatment options.

c. The analytical and functional characteristics of the diagnostic methodology based on galectin/CD44 proteins as specific biomarkers for the hematologic malignancies indication have been demonstrated in a controlled laboratory setting, and testing on appropriate clinical samples has been initiated. Target biomarkers were validated based on clinical samples from human patients in cooperation with external laboratories and research groups.

For the therapeutic indications

i. Using disease-specific human galectin proteins will not require the lengthy development and very expensive process of humanization required by murine antibodies.

ii. Use of human proteins can shorten the regulatory processes for clinical trials by appropriate authorities such as FDA and EMA.

iii. Using disease-specific CD44 proteins; the genetic alteration, found in CD44 proteins in different hematologic malignancy conditions, results the translation of a modified protein, which confers a biological advantage upon the destructive cancer cells, but may be used therapeutically to target these cells. We will develop monoclonal antibodies that recognize the genetically-modified proteins, but do not interact with the corresponding proteins of normal cells that do not contain this genetic alteration. This platform discovery can be applied to produce therapeutics for a large number of major, costly diseases.

iv. Low side effects; disease-specific galectin proteins and/or anti-CD44 mAbs, as a therapeutic approach, for different hematologic malignancies has a huge potential to reduce the side effects of the treatment compared to current drugs in the clinical use.

v. The manufacturing process of production and purification of galectins in bacterial systems will be very fast and cheap compared to production of other biological response modifiers such as antibodies. The newly developed drugs expected to be significantly cheaper for customers.

vi. For the galectin compounds; time has a very important role in conferring high commercial value. Short development periods provide increased time for patent validation, increasing incomes and commercial benefits potentially by 2-3 years.

Summary

There is currently a marked lack of clinical useful disease - and process - specific biomarkers in the field of hematologic malignancies

which is hampering progress towards optimal approaches to treatment sequence and most effective management of these conditions. Our research provides unique opportunity to develop novel innovative diagnostic kit based on previously identified and validated biomarkers for early diagnosis of different hematologic malignancy conditions within a clinical research setting. Such novel innovative product has huge commercial potential for short-term uptake (within five years) in the clinic and offers a platform for further diagnostic, biomarker and therapeutic developments for the benefit of human patients.

Acknowledgments

None.

Conflicts of Interset

None.

References

1. Debra AH, Alexandra GS, Andrew J, et al. Time-to-diagnosis and symptoms of myeloma, lymphomas and leukaemias: a report from the Haematological Malignancy Research Network. *BMC Hematology.* 2013;13:9.

2. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood.* 2009;114 (5):937–951.

3. *World Cancer Report 2014.* World Health Organization. USA, 2015. p. 13.

4. Guttmacher AE, Collins FS. Molecular diagnosis of the hematologic cancers. N Engl J Med 348: 1777-1785.

5. Juo Pei-Show. *Concise Dictionary of Biomedicine and Molecular Biology.* Hoboken: CRC Press, USA, 2001. p. 629–666.

6. *Cancer Rehabilitation Medicine Quick Reference (RMQR).* New York: Demos Medical Publishing, USA, 2009. p. 181.

7. Horner MJ, Ries LAG, Krapcho M, et al. *SEER Cancer Statistics Review, 1975-2006.* Surveillance Epidemiology and End Results (SEER). Bethesda, MD: National Cancer Institute, USA. 2009.

8. Charles MF, Randy CA. The Clinical and Economic Value of Rituximab for the Treatment of Hematologic Malignancies. *Contemporary Oncology.* 2011;1–9.

9. Golan I, Nedvetzki S, Melnik L, et al. Expression of extra trinucleotide in CD44 variant of rheumatoid arthritis patients allows generation of disease-specific monoclonal antibody. *Journal of Autoimmunity.* 2011;28(2-3):99–113.

10. Eshkar Sebban L, Ronen D, Levartovsky D, et al. The Involvement of CD44 and Its Novel Ligand Galectin-8 in Apoptotic Regulation of Autoimmune Inflammation. *The Journal of Immunology.* 2007;179(2):1225–1235.

11. Golan I. The Role of Galectin Proteins in the Induction of Apoptosis in Arthritic Joints; Routes for New Therapies for Autoimmune Diseases and Cancer. *MOJ Immunol.* 2015;2(1):00035.

12. Nedvetzki S, Golan I, Assayag N, et al. A mutation in a CD44 variant of inflammatory cells enhances the mitogenic interaction of FGF with its receptor. *J Clin Invest.* 2003;111(8):1211–1220.