unique molecular genetic features, and in some cases, the therapeutic interventions. ET probably carries the lowest rate of transformation to acute myeloid leukaemia (AML), whereas MF may carry a relatively high risk; lymphoid transformation has been reported in rare cases. The risk of transformation in CML to BC in the *ABL1*-tyrosine kinase inhibitors (TKI) era appears to be quite low, <2% per annum. Transformed disease in general tends to be difficult to be managed and is associated with a poor prognosis. The best treatment strategy, therefore, remains the prevention of transformation. Allogeneic stem cell transplantation is currently the only treatment that has been observed to confer long-term benefit to a small minority of patients who qualify for it. In this presentation, I will address the evolving genetic landscape, translational research efforts and investigational therapies for transformed MPNs.

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SP 16

The new European leukemianet recommendations for treating CML

Rüdiger Hehlmann

Twenty-two years after the first patients with chronic myeloid leukemia (CML) were treated with the tyrosine kinase inhibitor (TKI) imatinib, outcome exceeds all expectations: the vast majority of CML patients have achieved normal life expectancy and some patients in sustained deep molecular remissions (DMR) may even be operationally cured in durable treatment-free remissions (TFR). However, some expectations remain unmet. Most patients are not yet cured and require life-long maintenance therapy. Also, progression to blast crisis still occurs in 5–7% of patients and remains a challenge. CML has not become the expected model disease for treating other leukemias or cancers, but the principle of elucidating the pathogenesis as a successful approach for cancer treatment has been impressively demonstrated in CML.

New insights have emerged from maturing long-term academic and commercial clinical trials regarding optimum management of CML. Velocity of response has unexpectedly proved less important than hitherto thought, does not predict survival, and is of unclear relevance for TFR. Serious and cumulative toxicity has been observed with TKI that had been expected to replace imatinib. Generic imatinib has become cost-effective first-line treatment in chronic phase despite chronic low-grade side-effects in many patients. Earlier recognition of CML end-phase by genetic assessment might improve prospects for blast crisis. Treatment discontinuation and TFR has become an important new treatment goal of CML. Duration of DMR (MR4, MR4.5) may be the best predictor of success. To reflect this new situation, the European LeukemiaNet has recently revised and updated its recommendations for treating CML. The presentation will focus on recent developments and on current evidence for treating CML in 2020.

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SP 17

Ex vivo activation of pleural T cells in pleural malignancies

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Introduction: MPE are uniformly fatal. It is estimated that the incidence of MPE in the United States is more than 150,000 cases per year, making this a common terminal pathway for a variety of cancers and a dire problem without a solution. Currently available cellular therapeutics are costly and often lack polyclonality, polyfunctionality, and the ability to persist as central memory. The treatment of this deadly complication is potentially at a turning point if the rich immune infiltrates that characterize the majority of effusions can be redirected to an efficacious anti-tumor response. Despite this promise, pleural immune infiltrates have not been used to generate effector cells for adoptive cellular therapy.

Objectives: We have exploited the heterogeneous cellular composition of MPE by piloting the generation of therapeutic T-cell products, using conventional methods used for expanding tumor-infiltrating lymphocytes (TIL). The advantages of plural T cells are: (1) Fewer cycles of expansion owing to several orders of magnitude greater starting number of T cells; (2) Greater initial clonal and functional heterogeneity; (3) Likelihood of preserving polyclonality, polyfunctionality and central memory.

Results: MPE have abundant tumor infiltrating CD3+ T-cells, CD19+ B-cells, CD14+ macrophages, and EpCAM-/Cytokeratin+ mesothelial cells. Regulatory T-cells, which may be abundant in TIL, are low or absent in MPE. Our laboratory's average recovery of viable nucleated cells per MPE is $7.8 \pm 4.0 \times 10^8$ cells, with viability exceeding 95%. The cellular composition (tumor, lymphocytes, macrophages, neutrophils, mesothelial cells) varies from patient to patient, but T-cell recovery averages $2.0 \pm 1.6 \times 10^8$ (mean, SD). In pilot experiments we cultured whole breast cancer MPE in the presence of anti-CD3/anti-CD28 Dynal beads, IL-2 and IL-7 for 96 h. CD3+ T cells were FACS-sorted and added to autologous tumor monolayer cultures and expanded for an additional passage (2 weeks). Expanded passage 2 T cells were compared to freshly isolated T cells (2nd MPE drainage) for ability to kill autologous tumor and non-tumor targets (live cell imaging). Expanded T cells were potently cytotoxic, whereas freshly isolated MPE had no activity against autologous tumor. Expanded T cells did not kill the autologous non-tumor target (adherent cells isolated from peripheral blood). Additionally, we tested freshly isolated breast cancer MPE T cells for the ability to secrete cytokines associated with expansion and effector generation (IL-2, IFNγ and TNFα). We also measured the immunosuppressive cytokine IL-10. Freshly isolated plastic nonadherent cells from a breast cancer MPE were incubated with TPA+ ionomycin for 1 h, followed by brefeldin for 2 h. CD4+ T cells (85%) and CD8+ T cells (9%) were gated on cells co-expressing intracellular IL-2 and IFNγ. Polyfunctional T cells, defined as IL-2+/IFNγ+/TNFα+/IL-10-, comprised 0.38%, and 0.82% of CD4+ and CD8+ T cells. Unstimulated control cultures constitutively secreted IL-10 and IFNγ but not IL-2 or TNFα.

Conclusions: Pleural infiltrating T-cells represent an attractive source of T cells for immunotherapy. They are numerous, readily expandable without protracted passage and can be induced to secrete immunostimulatory and effector cytokines and specifically kill autologous tumor.

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SP 18

Are there really cancer stem cells and how do they operate?

Robert Gale

Some but not all data suggest within a cancer not all cancer cells are the same, namely, there are diverse cell types. The *stem cell* theory of cancer proposes amongst all cancer cells a very few act as *stem cells*. These cells reproduce themselves and sustain the cancer much like normal stem cells renew and replenish organs and tissues like the haematopoietic system. There are important therapy implications if cancers are really driven by a few *stem cells*. For instance, many anti-cancer therapies are evaluated based on their ability to make a cancer smaller. This can happen without killing cancer *stem cells*. If so, the cancer is likely to recur, perhaps in a more dangerous form such as metastases. In fact, most people with cancer die from metastases, not the primary cancer. The analogy is selecting a more virulent microbe by indiscriminate use of antibiotics.

One component of the cancer *stem cell* theory concerns how cancers arise. Typically, for a cell to become cancerous it must accumulate substantial numbers of mutations. A leukaemia such as chronic myeloid leukaemia (CML) is an exception caused by 1 mutation (*BCRABL1*). Conventional cancer theory is that any cell has the potential to become a cancer. However, other data suggest only some cells, those with *stem cell* potential, can develop into a cancer. This may explain why some normal people can have cancer-related mutations without having cancer, for example normals with *BCRABL1* or normals with t(14;18) without CML or without a lymphoma. The hypothesis is the cell(s) in which these mutations occur are not *stem cells* and therefore lack the potential to cause cancer. However, we must also consider the possibility some mutations can re-programme a cell without *stem cell* potentially to become a *stem cell*. An example of this are induced pluripotent stem cells iPSC) which are adult (non-stem) cells reverted to an *embryonic stem cell* state by introducing 4 genes. Another notion is only cells with *stem cell* like features survive sufficiently long to accumulate the typically large number of mutations required for cancer development. The theory, therefore, is cancer *stem cells* arise from normal *stem cells* or *precursor cells* produced by normal *stem cells*.

Another important implication of the cancer *stem cell* theory is cancer *stem cells* are closely related to normal *stem cells* and share many properties. Cancer cells produced by cancer *stem cells* should follow many of the rules observed by normal daughter cells. In this regard cancer cells can be considered a caricature of normal cells with similar but distorted features. If so, it may be possible to use knowledge about normal *stem cells* to identify and attack cancer *stem cells*.

Lastly, it may not be necessary to eradicate all cancer stem cells to cure a cancer. For example, in CML, therapy with tyrosine kinase-inhibitors (TKIs) markedly reduces numbers of mature leukaemia cells but not any and certainly not all CML *stem cells*. Regardless, in a substantial proportion of people with CML responding favorably to TKI-therapy it is possible to stop therapy without leukaemia returning. In sum, increasing knowledge of cancer stem cells should improve our understanding of and ability to treat diverse cancers.

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SP 19

Challenges in treating solid tumors in developing countries

Adnan Abdul Jabbar

There is an increasing number of cancers worldwide due to epidemiological transition. Longer life spans resulting in aging population is among some of the reasons for growing burden in cancer worldwide. The number of new cancer cases is expected to increase by nearly 75% by 2030 (107,000 additional cases per annum), with 60% of cases in the elderly (aged ≥65). The extent of cancer related morbidity and mortality is directly linked to the effectiveness of efforts to prevent, control and treat cancer, particularly in the developing world. In 2012, almost 57% of all cancer cases and 65% of cancer deaths occurred in low-and middle-income countries. If the current trend continues, the burden of cancer will increase to 22 million new cases annually by 2030, with 81% of new cases and almost 88% of mortality occurring in less developed countries. Cancer care in a country like Pakistan is challenging because of lack of strategic information and national planning for cancer control. Cancer registry provides important information that helps in directing and planning cancer prevention and care. Lack of national cancer registry limits estimation of true burden, identification of areas that require special need and thereby proper treatment strategy. Health systems required to deliver comprehensive life-saving treatments are limited in the country. Out of pocket payments and private health care usage remains high. A number of patients are not covered by insurance and individuals face catastrophic expenditure in seeking treatment. As a result, there is disparity in access to quality care. High incidence of later stage disease is very common due to social stigma associated with cancer treatment, myths, lack of awareness and preference for alternative treatment options. Drugs that have lately revolutionized cancer management are either not available in the country and if present, are extremely expensive for a common person to afford. Palliative care and access to supportive care medicines is almost nonexistent. Pain management is restricted to analgesics without narcotics. With cancer rates steadily rising in low- and middle-income countries, the disease will inevitably