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EDITORIAL

Checkpoint inhibitors and radiation treatment in Hodgkin's lymphoma

New study concepts of the German Hodgkin Study Group

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Abstract
Background Patients with classical Hodgkin's lymphoma (cHL) have a good prognosis even in advanced stages. However, combined chemo- and radiotherapy, as the standard of care, is also associated with treatment-related toxicities such as organ damage, secondary neoplasias, infertility, or fatigue and long-term fatigue. Many patients suffer from this burden although their cHL was cured. Therefore, the efficacy of immune checkpoint inhibitors like anti-PD1/PD-L1 antibodies in the treatment of solid cancers and also in HL offers new options. A remarkable and durable response rate with a favorable toxicity profile was observed in heavily pretreated cHL patients.
Methods Planning to perform prospective randomized clinical trials in the content of radio-immune treatment in patients with Hodgkin's lymphoma (HL), we transferred the results of preliminary clinical studies and basic research in clinical relevant study concepts.
Results Based on these promising early phase trial data, the German Hodgkin Study Group (GHSG) will investigate innovative treatment regimens in upcoming phase II trials.
Conclusion The therapeutic efficacy and potential synergies of anti-PD1 antibodies in combination with chemo- or radiotherapy will be investigated in various settings of HL.

Keywords Organs at risk · Immune modulation · Radioimmune therapy · Abscopal effect · Programmed cell death protein 1

Checkpointinhibitoren und Strahlentherapie bei Hodgkin-Lymphom

Neue Studienkonzepte der Deutschen Hodgkin Studiengruppe

Zusammenfassung
Hintergrund Patienten mit einem klassischen Hodgkin-Lymphom (cHL) haben über alle Stadien hinweg eine gute Prognose. Allerdings treten unter der kombinierten Therapie mit Chemotherapie und Bestrahlung therapieabhängige Toxizitäten wie z. B. Organschäden, Sekundärtumoren, Fatigue oder Langzeit-Fatigue auf. Viele Patienten leiden trotz einer Heilung an diesen Symptomen. Daher bietet die nachgewiesene Wirksamkeit der Anti-PD1/PD-L1-Antikörper bei soliden Tumoren, aber auch beim HL neue Behandlungsoptionen. Bei intensiv vorbehandelten Patienten mit rezidiviertem cHL wurde bei guter Verträglichkeit eine hohe Ansprechrate mit z. T. langanhaltenden Remissionen beobachtet.
Methoden Im Rahmen der Planung prospektiver randomisierter Studien im Zusammenhang mit Radioimmuntherapie bei Patienten mit Hodgkin-Lymphom wurden Ergebnisse erster klinischer Studien und Daten der Grundlagenforschung in klinische relevante Studienkonzepte eingebunden.

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Ergebnisse Basierend auf diesen vielversprechenden Ergebnissen aus Frühphasestudien prüft die Deutsche Hodgkin Studiengruppe (GHSG) in naher Zukunft innovative Behandlungskonzepte in Phase-II-Studien.
Schlussfolgerung Die therapeutische Effektivität und mögliche Synergismen von Anti-PD1-Antikörpern mit Chemo- und Strahlentherapie werden zukünftig in unterschiedlichen klinischen Konstellationen des cHL evaluiert.

Schlüsselwörter Risikoorgane · Immunmodulation · Radioimmuntherapie · Abskopaler Effekt · PD-1

Background

Programmed death 1 (PD-1) protein and one of its ligands, PD-1-L1/-L2, play a pivotal role in self-tolerance and regulation of immunity. PD-1 is expressed on T- and B-lymphocytes as well as on monocytes, macrophages, and natural killer cells [1]. PD-1-L1/2 are commonly presented on antigen-presenting cells and in varying degrees on tumor cells. Both PD-1-L1 and -2-binding with PD-1 results in an inhibitory reaction on activated T-lymphocytes. Tumor cells exploit this pathway to evade a sufficient response by the host's immune system.

Blockade of interactions between PD-1 and PD-1-L1 enhances immune function and mediates the antitumor effect. PD-1-blocking antibodies have been used to enhance immunity in solid tumors and obtain remarkable clinical responses with an acceptable toxicity profile [1]. Programmed death-receptor (PD-1) is presented on T- and B-lymphocytes as well as on monocytes, macrophages, and natural killer cells [2]. Their ligands PD-L1/2 are presented on antigen-presenting cells. Both PD-L1 and -2-binding with PD-1 results in an inhibitory reaction on activated T-lymphocytes. Classic Hodgkin's lymphomas (cHL) include small numbers of malignant Reed–Sternberg cells within an inflammatory and immune-cell infiltrate and therefore act as a target for anti-PD1 inhibition [3].

Initial data on nivolumab, a fully human monoclonal IgG4 antibody directed against PD-1, showed excellent response rates (Overall response rate: 87 %) in 23 patients with relapsed or refractory cHL with tolerable treatment related toxicity [4, 5]. Treatment-related rash, thrombocytopenia, pancreatitis, pneumonitis, stomatitis, colitis, gastrointestinal inflammation, thrombocytopenia, increased lipase levels, a decreased lymphocyte level, and leukopenia were documented. No grade 5 toxicity occurred [4].

An attractive option seems to be the combination of checkpoint inhibiting therapy with other modalities: To combine the checkpoint inhibitors with conventional cytotoxic agents or to combine different checkpoint agents. The third option for combination therapy is to administer checkpoint inhibitors with other types of immunotherapy, or with radiation therapy to produce synergistic antitumor activity [6].

Combination of anti-PD-1 antibodies with radiation therapy

Although chemotherapy and irradiation have historically been considered immunosuppressive, accumulating evidence emphasizes that the immune system plays an important role in the resultant tumor eradication [7]. Data showed that cytotoxic treatments have immunostimulatory effects on tumor cells and their microenvironment [8, 9]. The changes in the immune profiles of patients treated with radiation and immunotherapy with—the so-called abscopal effect—was described recently and underlined with impressive clinical data in melanoma treatment [10, 11]. As mentioned before these results are well known from preclinical data [12–14] and there is still little knowledge why the effects are seen frequently in mice models and rarely in oncologic patients.

Rationale for use in early stage Hodgkin lymphoma

Over the last two decades, the major efforts were focused on decreasing the number of chemotherapy cycles and radiation therapy volume and/or radiation dose for patients with early stage cHL, incorporating positron emission tomography (PET) imaging in diagnostic, prognostic, and treatment planning. Early stage cHL is a well curable disease and treatment is a combination of chemotherapy and consolidating radiotherapy. Based on the results of the GHSG HD10 and HD13 trials in early stage favorable cHL of the German Hodgkin Study Group two cycles of ABVD followed by 20 Gy involved field radiotherapy (IF-RT) are a widely accepted standard of care. Results from these studies showed long-term PFS rates of over 90 % [15, 16] with very small room for further improvement. Therefore the innovation and development in treatment technics of radiotherapy have to be evaluated for avoiding long-term side effects [17].

More recently, the improved knowledge of the molecular biology of the disease led to the development of highly active new agents. Accordingly, the current efforts are focusing on incorporating these new agents into standard of care regimens, aiming at ongoing good cure rates, while reducing treatment-related toxicity. Treatment-related toxicity for cHL is reported low, but many patients concern fatigue and long-term fatigue after completion of treatment. In the past underestimated, one of the most striking long-

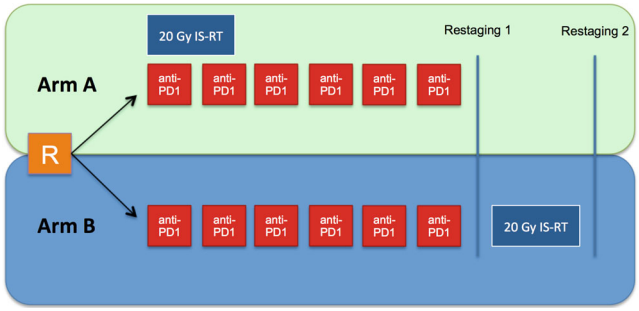

Fig. 1 Flow chart of "Anti-PD-1 antibody treatment and radiotherapy in early stage favorable cHL". Anti-PD1 therapy with simultaneous (*Arm A*) versus consolidating (*Arm B*) involved-site radiation (*IS-RT*); *PD1* anti-PD1-antibody

term toxicity is chronic fatigue (CF). The prevalence of CF is 2.5–3 times higher in long-term cHL survivors than in the general population [18]. In a systematic overview Daniels et al. [19] showed prevalence rates of 11–76 % in Hodgkin survivors, compared to 10 % in the general population. Its occurrence at young age and the increasing numbers of long-term survivors reporting long-lasting fatigue have prompted increased interest in this subject. One possibility to decrease CF rates could be the (partial) replacement of chemotherapy by new substances in the treatment of cHL.

New concepts—new questions

The use of antibodies blocking the PD-1/PD-L1 pathway in the context with radiation treatment may open new horizons in the treatment of HL. Several aspects remain unclear:

- The optimal schedule with radiation: concomitant versus sequential.
- The optimal dose of radiation therapy: standard doses of 20 and 30 Gy versus lower doses.
- The optimal fractionation regimen: conventional versus hypofractionated.

Upcoming GHSG studies with anti-PD1 and radiotherapy in cHL

The study "Anti-PD-1 antibody treatment and radiotherapy in early stage favorable cHL" will include patients with early stage favorable cHL without any risk factors. In both arms of this multicenter phase II trial, patients will be treated with 6 cycles of an anti-PD1 antibody and 20 Gy involved site radiotherapy (IS-RT). One hundred patients will be included into this study. Mature results are expected after 2 years of median follow-up time. In Arm A IS-RT is given *simultaneously* with anti-PD1. In Arm B IS-RT starts *after* completion of 6 cycles of anti-PD1 and restaging evaluation. Study objectives include efficacy, tolerability, feasibility, and detailed analyses of quality of life for these chemotherapy-free combination regimens. Target and treatment volumes are defined according to data of major clinical trials and international guidelines on lymphoma treatment [20]. IS-RT will be used in both treatment arms (Fig. 1). From the radiation oncologists' point of view this innovative study implicates questions on tolerability and efficacy in the simultaneous versus sequential setting, and for future considerations on dose and treatment volumes for future studies.

Pretreatment PET-CT in treatment position and new radiation techniques are mandatory.

In patients with diagnosis of early stage unfavorable HL, a combination of chemo- and anti-PD-1-based therapy will be investigated in the multicenter phase II trial "Nivolumab and AVD in early stage unfavorable cHL" (NIVAHL). Outcome in this group with risk factors (elevated ESR, extranodal spread, large mediastinal mass and involvement of ≥3 lymph node regions) is already inferior to the favorable risk group and full replacement of classical chemother-

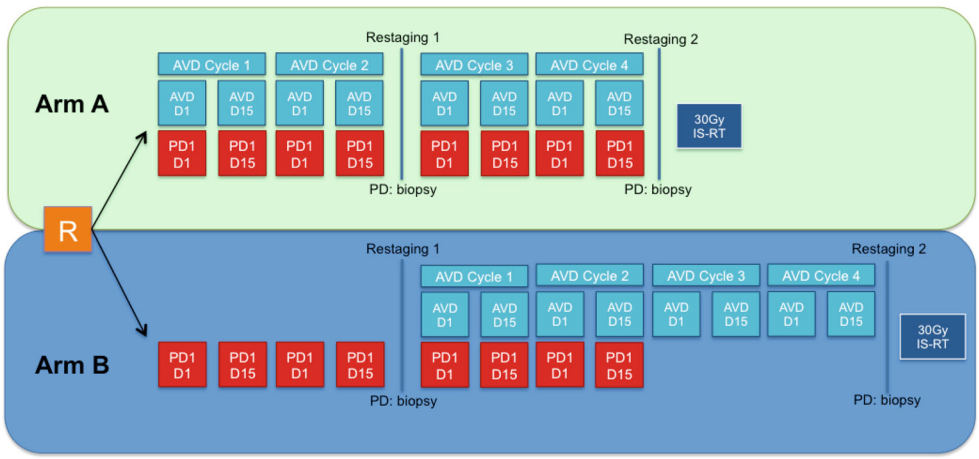

Fig. 2 NIVAHL trial in early stage unfavorable cHL: 4 × nivo–AVD (Arm A) and 4 × nivo + 2 × nivo-AVD + 2 × AVD (Arm B) followed by 30 Gy IS-RT (Arm A and B); *AVD* Adriamycin, Vinblastin, Dacarbazine; *PD1* anti-PD1-antibody

apy is not yet feasible. The potential synergistic immunogenic activity of AVD (omission of bleomycin to reduce potential risk of pneumonitis) and the anti-PD-1 antibody nivolumab will be evaluated in a total of 100 patients. For patients in Arm A, four simultaneous cycles of AVD and nivolumab are administered, while patients in Arm B will initially be treated with a nivolumab monotherapy lead-in. Treatment continues after an interim staging with two cycles nivo–AVD followed by two cycles of AVD without nivolumab (Fig. 2). Primary endpoint is the complete response rate and treatment related morbidity will serve as a key secondary endpoint. Further endpoints include efficacy measures such as OS and progression-free survival and detailed analyses of quality of life. Consolidating treatment will be 30 Gy IS-RT in both arms.

Conclusion and future directions

Working on Hodgkin's lymphoma as a radiation oncologist means, on the one hand, to evaluate long-term side effects of radiotherapy and performing quality assurance [21–23]. While on the other hand, it is about integrating modern radiotherapy concepts in novel treatment strategies like immunotherapy.

In conclusion, the above presented clinical trial projects implement novel anti-PD1 therapy into first-line treatment of early stage (un-)favorable cHL. They will investigate efficacy and potential of anti-PD1 antibody to reduce treatment-related morbidity, especially chronic fatigue. Furthermore, they will explore questions on the optimal schedule of anti-PD1 antibody treatment with or without chemo- or radiotherapy and the eligibility and validity of classic concepts in target volume definition, fractionation, and dose prescription for radiation therapy. Less chronic fatigue, but probably new treatment-related toxicities are expected. Even more importantly, the immune-modulating potential of radiotherapy in combination with anti-PD1 antibodies can be characterized for the first time in a randomized clinical trial.

A potential abscopal effect of localized RT in combination with nivolumab will be investigated in a different upcoming phase II GHSG trial in cHL patients progressing on anti-PD1 therapies. All study concepts are accompanied by a comprehensive set of translational and immunological analyses on tumor tissue and blood samples.

Compliance with ethical guidelines

Conflict of interest C. Baues, R. Semrau, U.S. Gaipl, P.J. Bröckelmann, J. Rosenbrock, A. Engert, and S. Marnitz state that they have no competing interest.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

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