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Current Perspective

State of clinical research of radiotherapy/chemoradiotherapy and immune checkpoint inhibitor therapy combinations in solid tumours—a German radiation oncology survey

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Abstract Combinations of immune checkpoint inhibitors (ICIs) with radiotherapy and/or chemoradiotherapy are currently under investigation in many cancer types and clinical settings. In this survey, we solicited members of the German Radiation Oncology Society and young DEGRO (working group of DEGRO e.V.) to review the current status of research in this field and underline critical issues such as oncological benefit, treatment toxicity and obstacles in clinical research. The responses represent 14 different departments of radiation oncology at German university hospitals. Respondents of the same department were analysed for congruence. Sixty-one percent of all respondents perform radiotherapy/chemoradiotherapy and ICI therapy combination studies at their institutions and participate in multicentre studies. Combinations were investigated mainly in head and neck tumours (95%), lung cancer (57%), malignant melanoma (48%) and tumours of the upper gastrointestinal tract (9%). Combination of chemoradiotherapy with checkpoint inhibitors was only tested in head and neck cancers (52%), non–small-cell lung cancer (NSCLC) (8.70%) and malignant melanoma (4%). A combination of radiotherapy/chemoradiotherapy with ICIs is assumed to be effective or very effective by >85% of all respondents. The treatment of intracranial metastatic disease by this combination is assumed to be very effective by most respondents (61%). The present survey shows great acceptance of new combined modality treatment paradigm. ICIs with

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radiotherapy and/or chemoradiotherapy are under investigation at >75% of all participating centres. Head and neck tumours, NSCLC and malignant melanoma are the most frequently tested cancer types.

1. Introduction

Immune checkpoint inhibitors (ICIs) have been shown to be an effective treatment modality and are used in several solid cancer types and clinical settings [1–5]. ICI therapy is thought to have fewer side-effects than chemotherapy and is a potential option for those who have cancer that is resistant to conventional treatment modalities. In recent years, monoclonal antibodies blocking the cytotoxic T-lymphocyte–associated protein 4 and programmed cell death protein 1 and its ligand have made a significant impact on cancer patients' prognosis, conferring improved survival and boosting the development of tumour-directed immunotherapy in general.

Radiotherapy (RT) is an established treatment modality for cancer with the aim of providing local control. Increasing evidence demonstrates that RT is able to trigger an anti-tumour immune response that can lead to an immune-mediated regression in- and outside of the irradiated target lesions [6]. It is assumed that RT is able to induce an immunogenic cell death and counteract an immune-suppressive tumour microenvironment to effectively convert the irradiated tumour into an in situ vaccine for both local and systemic disease control [7].

Conventional chemoradiotherapy (CCRT) shows improved local and systemic control in comparison with RT alone in several types of cancer [8–10]. Furthermore, CRT has been identified to cause increased inflammation and immune modulation compared with RT alone [11]. In the last decade, the immunological aspects of CRT have been thoroughly investigated in preclinical studies, and as a result, combinations of ICIs with radiation and CRT are currently under investigation [5,12]. Actually, there are more than 900 prospective studies ongoing concerning the combination of RT with ICI [7,13].

In the general community, experience with combinations of RT/CRT and ICIs is low and has not been previously evaluated. In view of the paucity of published literature, we decided to perform a clinical research survey investigating RT/CRT and ICI therapy combinations in Germany.

To the best of our knowledge, this is the first survey reviewing the current status of RT, CRT and ICI combinations, underlining critical issues such as oncological benefit, treatment toxicity and obstacles in clinical research.

2. Methods

Survey design

The anonymous survey was designed with the online professional survey tool 'Umfrage Online' licenced for academic use. The survey contained eight questions with 33 multiple-choice items regarding the current studies at their institutions, clinical settings, e.g. cancer type and presence of brain metastasis, emphasising the oncologic benefit and obstacles of clinical research. An e-mail message with a link to the web-based questionnaire was sent to 43 selected members of the German society for radiation oncologists (Gesellschaft fuer Radioonkologie e.V. [DEGRO]) at different departments of radiation oncology at German (university) hospitals or radiation biology/radiation oncology research institutions in Germany. The respondents are mainly members of the young DEGRO (working group of DEGRO e.V.) and are involved in clinical and experimental research at their institutions and represent experienced and active radiation oncologists/researchers. The survey invitation contained rationale, instructions on participation and contact information. The invitations were initially sent out on July 26, 2018 with a reminder ensuing on August 13, 2018 to maximise the response rate.

Respondents were instructed to select answers from a multiple-choice questionnaire.

Responses were collected from July to August 2018. Thirty-three multiple-choice items were evaluated, and all complete responses were deemed eligible for analysis using descriptive statistics. Ethical approval for a pattern of care study comprising an online questionnaire was not applicable.

Our findings were based on the responses of 23 experienced researchers/radiation oncologists.

3. Results

We received a total of 26 responses (62% response rate), of which 23 were completed and returned, hence eligible for further evaluation. The responders represent 14 different departments of radiation oncology at German university hospitals. Fourteen (61%) responders perform RT and ICI therapy studies at their institutions and participate in multicentre studies. Additionally, four (17%) responders are only involved in multicenter

studies investigating combinations of radiation and immune checkpoint inhibition.

Radiotherapy and ICI combinations were investigated mainly in head and neck tumours (95%), lung cancer (57%), malignant melanoma (48%) and tumours of the upper gastrointestinal (GI) tract (9%) (see Fig. 1). Combinations of CRT and ICI were only tested in head and neck cancers (52%), non-small–cell lung cancer (NSCLC) (9%) and malignant melanoma (4%). The oncologic benefit on overall survival, metastasis-free survival and local control of CRT and ICI combinations is assumed to be good or very good by >85% of all respondents.

In the treatment of cerebral metastases, the combination of RT and ICI therapy is assumed to be very good by 61% of all respondents (see Fig. 2).

The acute/late toxicity of this multimodal approach is rated as dangerous by 13 (13%) and moderately dangerous by 43 (35%) responders and of low risk by 44 (52%) of all respondents (see Fig. 3).

Financial resources are stated by 21 (91%), human resources by 18 (78%), lack of evidence by ten (44%) and lack of ethical committee approval by six (26%) of all respondents as most relevant obstacles for clinical research.

4. Discussion

The success of ICIs as a new treatment modality resulted in a widely and fast adoption in different types of cancer worldwide [1,2,14]. Currently, utilisation of ICIs is accompanied by intensive clinical research consisting of more than 900 ongoing clinical studies [7,13]. However, only a minority of the clinical trials investigating ICIs as a monotherapy in heavily pretreated patients have an acceptable long-term follow-up [15].

ICIs are only starting to be evaluated as an integral part of the combined multimodal approach, also including combinations with RT or CRT [1,5,7,14].

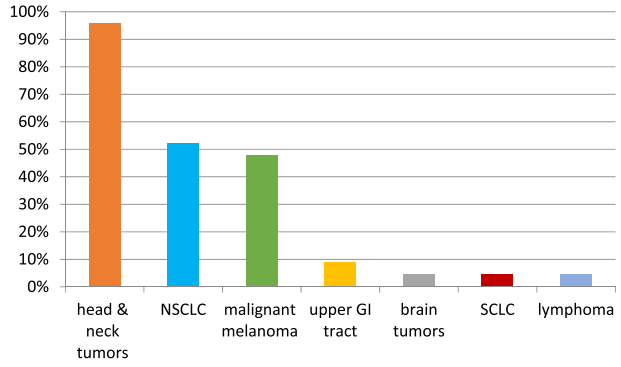

Fig. 1. Overview about investigated radiotherapy and immune checkpoint inhibitor therapy combinations at respondent departments. NSCLC, non–small-cell lung cancer; GI, gastrointestinal; SCLC, small-cell lung cancer. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

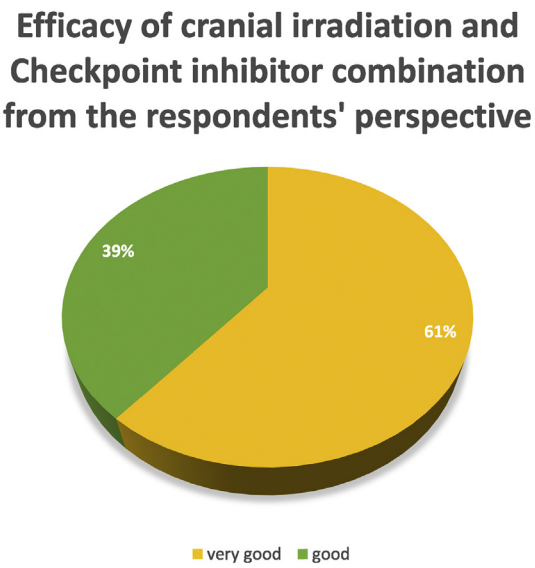

Fig. 2. Efficacy of cranial irradiation and checkpoint inhibitor combination from the respondents' perspective. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Importantly, the ongoing clinical trials investigating the combination of ICIs with other treatment modalities have mostly a single-centre non-randomised design and therefore, a relatively low impact for decision-making. Also, comprehensive characterisation of long-term oncologic benefit and late toxicity of this promising multimodal approach is at the moment lacking [16–18].

The present survey has demonstrated that the potential clinical relevance of this new multimodal approach could be emphasised while more than 60% of respondents perform RT and ICI therapy studies at their institutions and participate in multicentre studies concerning this issue. Current clinical trials are testing ICIs and RT or CRT combinations in several types of solid cancer and clinical settings [7]. In our survey, ICI and RT combinations were mainly investigated in head and neck tumours (95%), lung cancer (57%), malignant melanoma (48%) and tumours of the upper GI tract (8.7%). Combinations of CRT with ICIs were tested in head and neck tumours (52%), NSCLC (8.7%) and malignant melanoma (4%). The oncologic benefit such as overall and distant metastasis-free survival and local control is assumed to be good or very good by >85% of all respondents. This represents the great expectancy of multimodal treatment paradigm.

New or unexpected treatment-related side-effects may occur and have to be considered in combined approaches [17,19–21]. As a result, close monitoring for these patients is of essence. Acute/late toxicity of ICI therapy combined with RT/CRT was deemed as dangerous by 13 (13%), moderately dangerous by 43 (35%) and low by 44 (52%) respondents. This finding shows an ambiguous picture of expected toxicity of this combined approach.

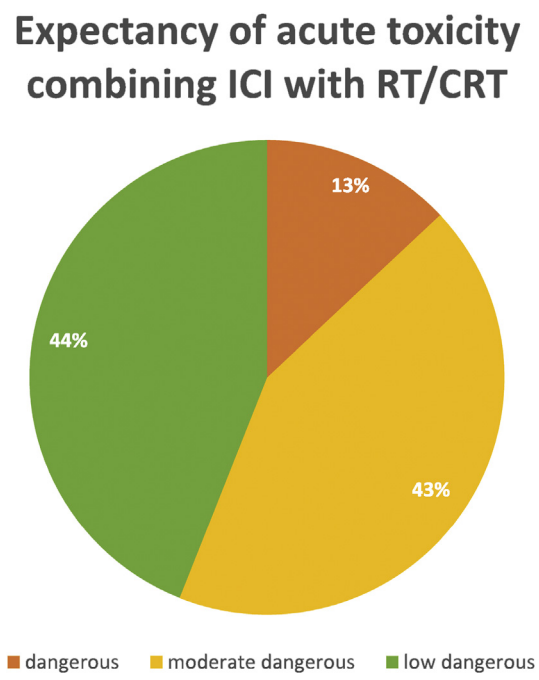

Fig. 3. Expectancy of acute toxicity combining ICIs with RT/CRT. CRT, chemoradiotherapy; ICI, immune checkpoint inhibitor; RT, radiotherapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Furthermore, increasing evidence seems to support the intracranial efficacy of ICIs in metastatic disease [18,22]. Based on retrospective studies, stereotactic RT (SRT)/ICI combination could improve local and distant intracranial control and overall survival [12,21,23]. In the treatment of brain metastases, the combination of SRT and ICIs is assumed to be very good by 61% of all respondents. In literature, the rate of severe neurological side-effects differs widely between 8.1 and 37.5% for SRT/ICI combinations [24]. Concretely, the combination could also result in higher rates of radionecrosis and intralesional haemorrhage [20,21].

An important point drawn from this survey is that clinical trials in this exciting new field of research need to be planned carefully. We asked our respondents about the obstacles of performing clinical trials of combining ICI and RT/CRT, and in general, financial (91%) and lack of human resources (78%) are the main issues that require addressing for further development of this research field.

To our knowledge, this is the first survey reviewing the current research status of RT/CRT and ICI combinations. The absolute majority of clinical trials in this field are performed at university hospitals; respondents are currently employed at 14 different departments of radiation oncology, and this presents a good overview of the latest research in RT/CRT and ICI therapy combinations.

Acknowledging the limitations of our survey, it is conceded that the number of respondents was, in general, low and needs to be considered when interpreting the results. However, the response rate is still acceptable with >60%. The selected respondents (two per radiation oncology department/research institution) are continuously involved in research programmes at their various institutions and represent experienced clinical research scientists.

5. Conclusion

The results of this survey give an overview of the current research status of RT/CRT and ICI combinations within the radiation oncology community in Germany and underline critical issues such as oncological benefit, treatment toxicity and obstacles in clinical research. This new multimodal approach is under investigation at >75% of all participating centres. Head and neck tumours, NSCLC and malignant melanoma are the most frequently tested cancer types.

Conflict of interest statement

None declared.

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Glossary

ICI: immune checkpoint inhibitor;
CRT: chemoradiotherapy;
DEGRO: Gesellschaft fuer Radioonkologie e.V.;
GI: gastrointestinal;
NSCLC: non–small-cell lung cancer;
RT: radiotherapy;
SRT: stereotactic radiotherapy