Hyperthermic Immunotherapy

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Complete clinical remission of stage IV breast cancer with bone and lymph node metastasis combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

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Advanced stage inoperable breast cancer has a poor prognosis and patients rarely enjoy durable complete response to treatment; progression free survival often is limited.

Methods
We previously reported complete remission of far advanced lung metastasis in triple negative breast cancer at ITOC3 (Munich) 2016 and complete remission of inoperable esophageal Cancer ITOC4 (Prague) 2017; here we report a similar successful treatment concept.

FD: 09/2016 in our clinic; the 65-γ female patient noticed the tumor about 10 years ago. She had always refused treatment. When she first presented in September 2016 she was diagnosed with a massive fungating exulcerating right breast carcinoma deeply infiltrating the anterior right chest wall with metastatic right axillary lymph adenopathy and metastasis to the right iliac bone and vertebral body L5 and T8. She underwent Tru-Cut biopsy which revealed invasive ductal carcinoma of no special type, G3, cT4 N1 M1 (bone), ER 100% and PR 40% positive, Ki–67 19%, HER-2/NEU (c- cerbB-2) neg. confirmed by FISH score 2+; the cancer was luminal A, EGFR neg., Tp53 neg., AR neg., PD-L1 and CTLA–4 overexpressed, TM CA 15-3 was elevated at 42 kU/l.

Additionally, soft tissue nodule upper lobe right lung suspicious for lung metastasis. Atelectasis changes in the lingula and lower lobes of the left lung, bilateral pulmonary embolism. Patient was on anticoagulants Tinzaparin 10.000 IE. When she was seen initially she presented with hemoglobin of 3.3 (!) and received 4 units of packed red blood cells. Karnofsky Index was 80%, moderate pain right chest, stable weight of 60 kg.

Social history: married, mother of 5 children; negative family history for cancer.

The patient initially presented with a very far advanced massive right sided breast cancer cT4 N1 M1 (bone) which was bleeding heavily upon slightest touch. The patient therefore underwent emergency palliative radiation 5 times between November 10 and November 17, 2016 with 25 Gy TD at 5 Gy single dose; additionally, she underwent immunotherapy as described previously combining low-dose checkpoint inhibitor ipilimumab−nivolumab in combination with low dose interleukin (IL-2) treatment parallel to local regional and whole-body hyperthermia. Additionally, low-dose metronomic chemotherapy was performed only twice combining gemcitabine (800mg/m2) and vinorelbine (30mg/m2).

Results
Unexpectedly, restaging at the end of January 2017 performed with clinical examination, bone scintigram, and CT thorax/abdomen and full laboratory workup proved complete remission of the primary large fungating breast cancer, complete remission of bone metastasis and massive shrinkage of lymphadenopathy with normal tumour markers. Telephone up in 07/2018 confirms Karnofsky score of 100%, pain or any other cancer related symptoms have vanished. Current (08/2018) follow-up time 22 months.
Conclusion
The unexpected remission of far advanced inoperable and metastatic breast cancer following a complex immunotherapy treatment including low-dose checkpoint inhibitors, hyperthermia and metronomic chemo-radiation therapy warrants further clinical studies. The presentation would include description of more cases and an overview of all treated patients.
Complete clinical remission of stage IV breast cancer with bone and lymph node metastasis combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever hyperthermia

Ralf Kleef a, Robert Nagy a, Viktor Bacher a, Hans Bojar b, Dwight McKee c, Ralph Mass d

INTRODUCTION

We previously reported complete remission of far advanced lung metastasis in triple negative breast cancer at ITCQ (Munich) 2016 and complete remission of inoperable esophageal cancer at ITCQ (Praha) 2017; hence we report a similar successful treatment concept.

The patient initially presented with a very far advanced massive right sided breast cancer (T4 N1 M1) which was bleeding heavily upon slightest touch. The patient therefore underwent emergency palliative radiation 5 times between November 10 and November 17, 2016, with 25 Gy TD at 5 Gy single dose; additionally, she underwent immunotherapy as described previously combining low-dose checkpoint inhibitor pembrolizumab in combination with low dose interleukin (IL-2) treatment parallel to local regional and whole body hyperthermia. Additionally, low-dose metronomic chemotherapy was performed only twice combining gemcitabine (800mg/m2) and vemurafenib (30mg/m2).

RESULTS

Unexpectedly, restaging at the end of January 2017 performed with clinical examination, bone scintigram, and CT thorax/abdomen and full laboratory workup proved complete remission of the primary large fungating breast cancer, complete remission of bone metastasis and massive shrinkage of lymphadenopathy with normal tumour markers.

Telephone up in 07/2018 confirms Karnofsky score of 100%, pain or any other cancer related symptoms have vanished. Current (08/2018) follow-up time 22 months.

STAGING

10/2016 before treatment

32/2016

09/2017

CONCLUSION

The unexpected remission of far advanced inoperable and metastatic breast cancer following a complex immunotherapy treatment including low-dose checkpoint inhibitors, hyperthermia and metronomic chemo-radiation therapy warrants further clinical studies.

MATERIALS & METHODS

FD: 09/2016 in our clinic; the 65-year female patient noticed the tumor about 10 years ago. She had always refused treatment. When she first presented in September 2016, the tumor was diagnosed with a massive fungating exulcerating right breast carcinoma deeply infiltrating the anterior right chest wall with metastatic right axillary lymph adenopathy and metastasis to the right iliac bone and vertebral body L5 and T8. She underwent Truecut Biopsy which revealed Invasive ductal carcinoma of no special type, G3, T4 N1 M1 (Bone), ER 100% and PR 40%, positive, Ki-67 19%, HER-2/NEU (c-erbB-2) neg, confirmed by FISH score 2+; the cancer was luminal A, EGFR neg., Trp53 neg., AR neg., PD-L1 and CTLA-4 underpressed, TIM3 15-18 was elevated at 43 kU/L.

Additionally, soft tissue nodule upper right lung suspicious for lung metastasis. Atelectasis changes in the lingula and lower lobes of the left lung, bilateral pulmonary embolism. Patient was on anticoagulants Tinzaparin 10,000 IE. When she was seen initially, she presented with hemoglobin of 3.3 (1) and received 4 units of packed red blood cells. Karnofsky index was 80%, moderate pain right chest, stable weight of 60 kg.

Social history: married, mother of 3 children; negative family history for cancer.

LITERATURE


AUTHOR AFFILIATIONS

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ICHS
36th Conference of the International Clinical Hyperthermia Society
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Hyperthermic Immunotherapy

Ralf Kleef, Vienna, Austria

36. Conference of the International Clinical Hyperthermia Society
28th-29th September 2018, Budapest, Hungary

Hyperthermic Immunotherapy
Learning objectives

- Fever and cancer
- Loco-regional versus whole-body hyperthermia
- Hyperthermic Immunotherapy in oncology
Epidemiology

In clear words:
Fever protects!

Fever– Harmful or beneficial?

4 Hypotheses
Fever– Harmful or beneficial?

1. Hypothesis: Evolution Studies [1].

Even cold-blooded animals can get fever, as a result they are looking for warmer waters or areas


Fever– Harmful or beneficial?

• 2. Hypothesis: Correlational Studies[2].

• Comparing the extent of the reaction fever temperature relative to morbidity and mortality.

All "fever"-Studies in humans and animals demonstrate the protective function of the fever

Fever– Harmful or beneficial?

• 3. Hypothesis: Antipyresis [3,4].

• Reduction of fever increases morbidity and mortality.


Fever– Harmful or beneficial?

4. Hypothesis: Hyperthermia [5-8].

Hyperthermia reduces morbidity and mortality and improves immunological functions

"I would cure all diseases if only I could produce fever"

Parmenides, Greek physician, 4th century BC

"Fever is "Body-Buildung" for the immune system."

Kleef, German physician, 21st century
William B. Coley (um 1888)

Julius Wagner-Jauregg

- 1927 the Austrian Julius Wagner-Jauregg was awarded the Nobel Prize for his fever therapy until then hardly curable syphilis in the final stage. He infected patients with malaria control to trigger the healing fevers.
- Hyperthermia by the means of the 19. century
Were the ancient physicians better?

Fever and cancer are inversley related

Spontaneous remissions were frequently associated with concurrent febrile infections


Chronic Infection or Inflammation and Cancer

- Chronic infection/inflammation engages leukocytes’ pro-inflammatory ‘tissue repair’ mode, resulting in ‘vicious cycle’ that:
  1. Promotes cancer initiation and development
  2. Suppresses immune function, including suppression of immune function of:
     - Macrophages
     - Neutrophils
     - Cytotoxic T cells
     - Natural Killer cells
     - B cells
Malignant inflammation

G. Stix

Following this brief introduction into fever and immunology we will now jump into clinical hyperthermia
Loco-regional hyperthermia

Issels R et al.

Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma

The EORTC 62961-ESHO 95 Randomized Clinical Trial

Reif D, Issels, MD, PhD, Lars H, Lindner, MD, Jaap Verweij, MD, Rüdiger Wessalowski, MD, Peter Reichardt, MD, Peter Wüst, MD, Pirus Ghadir, MD, Peter Hohenberger, MD, Martin Angele, MD, Christoph Salat, MD, Zejko Yuvasov, MD, Soeren Daugaard, MD, Clay Mella, MD, Ulrich Mansmann, MD, Hans Roland Dürr, MD, Thomas Knoel, MD, Sultan Abdel-Rahman, PhSc, Michael Schmidt, MD, Wolfgang Hiddemann, MD, Karl-Walter Jauch, MD, Claus Belka, MD, and Alessandro Gronchi, MD, for the European Organization for the Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group and the European Society for Hyperthermic Oncology.
WBH – Heckel HT 3000

WBH – Ardenne Iratherm 1000
Cell adhesion molecule mediated extravasation of immune cells following hyperthermia

Proposed mechanism of action:

**ICD – Immunogenic Cell Death induced by chemotherapy**

A series of immunogenic signals delivered by tumor cells undergoing ICD stimulates DCs to take up antigens from dying tumor cells.

“Cancer cells succumbing to ICD are de facto converted into an anticancer vaccine and as such elicit an adaptive immune response.”

But:

This specific immune effect is considerably counteracted by the general immune-suppressive effect of chemotherapy.
ICD – Immunogenic cell death

Hyperthermia releases Damage Associated Molecular patterns (DAMPS)

Gaipl (2011)
Rational for Immune therapy in Cancer Patients

- Disturbed immune system
- Inadequate immune reactions
- Immune cells are unable to detect tumor cells
Disclosures

RK has European and International patent pending

Low-dose checkpoint inhibitor therapy with interleukin-2 (IL-2) and fever range hyperthermia in stage IV cancer: a retrospective analysis with single case presentations

Ralf Kleef, Vienna, Austria

Presentation to 36. Conference of the International Clinical Hyperthermia Society
28th-29th September 2018, Budapest, Hungary
Every year 8.2 million deaths occur due to metastatic (stage IV) cancer worldwide.

Management of metastatic cancer is palliative by intent; even combination therapies with checkpoint inhibitors results in only a small minority (with the exception of metastatic melanoma) of durable responses, often at the cost of long lasting grade 3 and 4 autoimmune side effects.

Our team combines the following immunotherapies (with 52% clinical benefit rate in 98/119 evaluable patients; 38% Objective response rate):

1) Low-dose immune checkpoint blockade (LD-IC; ipilimumab plus nivolumab)
2) Individually titrated interleukin 2 (IL-2) treatment under Tauridine protection
3) Loco regional — and whole body hyperthermia without classical chemotherapy
4) If Chemotherapy: only after Chemo sensitivity testing and metronomic low dose chemotherapy

**IMMUNO-ONCOLOGY:**

Blocking CTLA-4 and PD-1 pathways with monoclonal antibodies

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CTLA-4 = cytotoxic T-lymphocyte antigen-4; PD-1 = programmed cell death 1; PD-L1/2 = PD ligand 1/2; TCR = T cell receptor.

**IMMUNE-CHECKPOINT BLOCKADE**

Immune-checkpoint blockade: antibodies targeting the negative regulatory molecules CTLA-4 and PD-1 to release the brakes on natural T cells responsive to tumor

Disadvantages

- **Tolerance breakdown** resulting in a high incidence of immune-related adverse events (irAEs)
- A meta-analysis in 1265 patients from 22 clinical trials found a respective incidence of **72% for all-grade immune-related adverse effects irAEs and 24% for high-grade irAEs** leading to hospitalization or intravenous treatment.
- The risk of developing irAEs in many clinical trials was **dependent of dosage**, with incidence of all-grade irAEs of 61% for ipilimumab 3 mg/kg and 79% for ipilimumab 10 mg/kg. Death due to irAEs occurred in 0.86% of patients.
- **Tumor regression is frequently associated with the development of autoimmunity**

**THERAPEUTIC PARADIGM SHIFT:**

The autoimmune effect of T cells should be exploited for the treatment of advanced cancer

- Breakthrough concept since irAEs associated with checkpoint inhibitors are considered primarily as severe safety issue (1, 2)
- **low-dose immune checkpoint inhibitor (LD-IC) combination** immune therapy demonstrated partial to complete remission in stage IV cancer patients (triple negative and hormone rec. pos. breast cancer, melanoma, bladder cancer and prostate cancer, (among others))
- LD-IC needs the Synergy of hyperthermia and fever

Proof-of-Principle retrospective analysis
Five best cases out of 119 intend-to-treat patients

- We report five cases of stage IV patients with solid carcinomas with far advanced metastases
- They had exhausted all conventional treatments
- They went into complete remission with low-dose IC (LD-IC) blockade in combination with individualized doses of IL-2 (ID-IL-2) treatment under Taurilidone protection and loco-regional and whole body hyperthermia but without classical chemotherapy.

Case 1.: COMPLETE CLINICAL REMISSION of Lung Metastases of Stage IV Triple Negative Breast Cancer Administering Low-Dose Immune Checkpoint Blockade in Combination with Hyperthermia and Interleukin-2

- 51 y.o. female with TNBC [ICD10: C50.9]
- Disseminated lung metastases [ICD10: C78.6]
- Malignant Lymphadenopathy [ICD10: R59.1]

- Karnofsky score of 70% (ECOG = 1)
- During inspiration severe pain in the left lateral chest wall
- Extreme Pain during sneezing
- Severe dyspnoea on exertion (DOE)
- Lack of appetite, insomnia, and exhaustion
- No more conventional treatments offered
Case 1.: RESULTS

Accepted for Publication: J. Integrative Cancer Therapies 08/2017; presented at ASCO Chicago 2016 and ITOC3 Munich, 2016

TNBC Pulmonary metastasis
Case 2.: COMPLETE PATHOLOGICAL RESPONSE (pCR) of stage IIIB oesophageal cancer combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

The patient was a 56-year-old male newly diagnosed with:
- Advanced uT4, N2, M0 inoperable adenocarcinoma of the distal esophagus [ICD10:C15.9]
- with disseminated mediastinal, sub/infradiaphragmal lymphadenopathy [ICD10: R59.1].
- MSI-low, Her-2-neu positive. He refused neoadjuvant chemotherapy, radiotherapy and chemo-radiotherapy

Presented at ITOC4, Prague, March 2017

Case 2.: COMPLETE PATHOLOGICAL RESPONSE (pCR) of stage IIIB oesophageal cancer combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

08/2016

10/2016
Case 2.: COMPLETE PATHOLOGICAL RESPONSE (pCR) of stage IIIB esophageal cancer combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

pCR was documented by 8 biopsies when re-endoscoped in 10/2016 after 8 weeks of primary combined immunotherapy

Case 3.: COMPLETE CLINICAL REMISSION of stage IV breast cancer chest wall recurrence combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

51y female, Local (chest wall) recurrence of her-2 neu pos. Breast cancer [C50.9]

• 08/2016 Chest wall recurrence, biopsied and proven to be recurrence of Her2-neu+ breast cancer, unresectable.
• Histology of recurrence was invasive ductal carcinoma grade 3 extending to the anterior inferior margin; also DCIS solid type nuclear grade 3 with microcalcification.
• Unfavorable high Ki–67 expression, p53 75% positive.
• Second opinion of radiation department: no radiation possible
Case 3.: COMPLETE CLINICAL REMISSION
of stage IV breast cancer chest wall recurrence combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

The 65 y female first presented in September 2016 with a massive fungating exulcerating right breast carcinoma deeply infiltrating the anterior right chest wall with metastatic right axillary lymphadenopathy and metastasis to the right iliac bone and vertebral body L5 and T8. She underwent Tru-Cut biopsy which revealed invasive ductal carcinoma of no special type, G3, cT4 N1 M1 (bone), ER 100% and PR 40% positive, Ki–67 19%, HER-2/NEU (erbB-2) neg, confirmed by FISH, Score 2+; the cancer was luminal A, EGFR neg., Tp53 neg., AR neg., PD-L1 and CTLA–4 overexpressed, CA 15-3 was elevated at 42 kU/l. When she was seen initially she presented with hemoglobin of 3.3 g/dl.

Patient underwent emergency palliative radiation 4 times (5Gy Per fraction) between November 10 and November 18, 2016. Additionally to our immunotherapy low-dose metronomic chemotherapy was performed only twice combining gemcitabine (800mg/m2) and vinorelbine (30mg/m2).

Unexpectedly, restaging at the end of January 2017 performed with bone scintigram, and CT thorax/abdomen and full laboratory workup proved complete remission of the primary large fungating breast cancer, complete remission of bone metastasis and massive shrinkage of lymphadenopathy with normal tumour markers.

Case 4.: COMPLETE CLINICAL REMISSION
of stage IV breast cancer with bone and lymph node metastasis combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

02.12.2016 08.03.2017
Case 4.: COMPLETE CLINICAL REMISSION of stage IV breast cancer with bone and lymph node metastasis combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

Late breaking abstract accepted for ESGO Vienna Nov. 2017
Case 5.: COMPLETE CLINICAL REMISSION
of stage IV breast cancer with bone, liver and lung metastasis
With low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

09/2014 grade 3 invasive ductal adenocarcinoma of the left breast, ER 100% percent positive, PR neg., Her2-neu neg. Patient underwent initial resection (02/2015) and neoadjuvant chemo radiation ACT, followed by aromatase inhibitor
07/2016 very large bone metastasis left scull, infiltrating to her dura mater; the patient underwent initial radiation; also new pulmonary metastasis.
08/2016 patient was started on Ibrance and aromatase inhibitor: PD.
09/2016 radiation of the cervical spine and T2.

10/2016 restaging with CT of the thorax and abdomen: stable lung metastasis but increasing pleural nodules; disseminated liver metastasis with index lesions between 2.1, 3.1 and 1.3 cm; new lytic osseous lesions are present; restaging of the skull with MRI indicated PD of the previously radiated left sphenoid lesion as well as PD of further lesions in the skull base and mandible. Bone scan indicates PD of all innumerous bony lesions.
11/2016-02/2017 – immune-thermotherapy two times following each other, and 3 cycles of topotecan chemotherapy.
03/2017 restaging with CT of Abdomen, pelvis and thorax demonstrated overall PR
06/2017 tumor markers decreased to the normal range.
05/2017 Restaging, MRI: overall stabilization and PR of the previously demonstrated disseminated metastasis in the skull and head.
08/2017 PET indicates CR

Case 5.: COMPLETE CLINICAL REMISSION
of stage IV Breast cancer with bone, liver and lung metastasis
With low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

10/2016  08/2017  10/2016  08/2017
Case 5.: COMPLETE CLINICAL REMISSION of stage IV Breast cancer with bone, liver and lung metastasis With low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

Side effect profile
Low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia in advanced cancer

Number of patients treated: n=119
**WHO I:** 30%  diarrhea, skin rash, nausea, headache
**WHO II:** 15%  diarrhea, skin rash, pneumonitis, elevated liver enzymes
**WHO III:** 7%
- 2 patients developed ulcerative colitis after 2 months controlled with corticosteroids
- 2 patients developed autoimmune thyroiditis controlled with hormone suppl.
- 2 patients developed autoimmune hepatitis controlled with corticosteroids
- 2 patients with pre-existing atrial fibrillation developed heart rhythm disturbances controlled with standard medical treatment (SMT)
**WHO IV:** 3 %
- 2 patients developed Diabetes mell. I treated with Insulin
- 1 patient developed AKI after 1 week and had to be transferred to dialysis
SUMMARY
Low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia in advanced cancer

Staging with iRECIST

Objective response rate - ORR 38%

Overall response – OR 52%

n= 98 of 119 evaluable

SUMMARY
Low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia in advanced cancer

Staging with iRECIST

Objective response number pat. n=37

TTP: not calculated n=4

Median Follow up: 14 month (3-33)
Great potential but…
more experience is needed

“The only way to increase the success rate is to double the rate of failures”
Thank you for your attention

www.dr-kleef.at