We can do better
- a patient perspective

Anne Sofie Boldsen Salicath

Bioethics of clinical innovation and unproven Methods
Copenhagen, 9 April 2019

Introduction

This is me. Summer of 2015.

A young and healthy mother of 4 kids (4-13y).
Married to a gorgeous man.

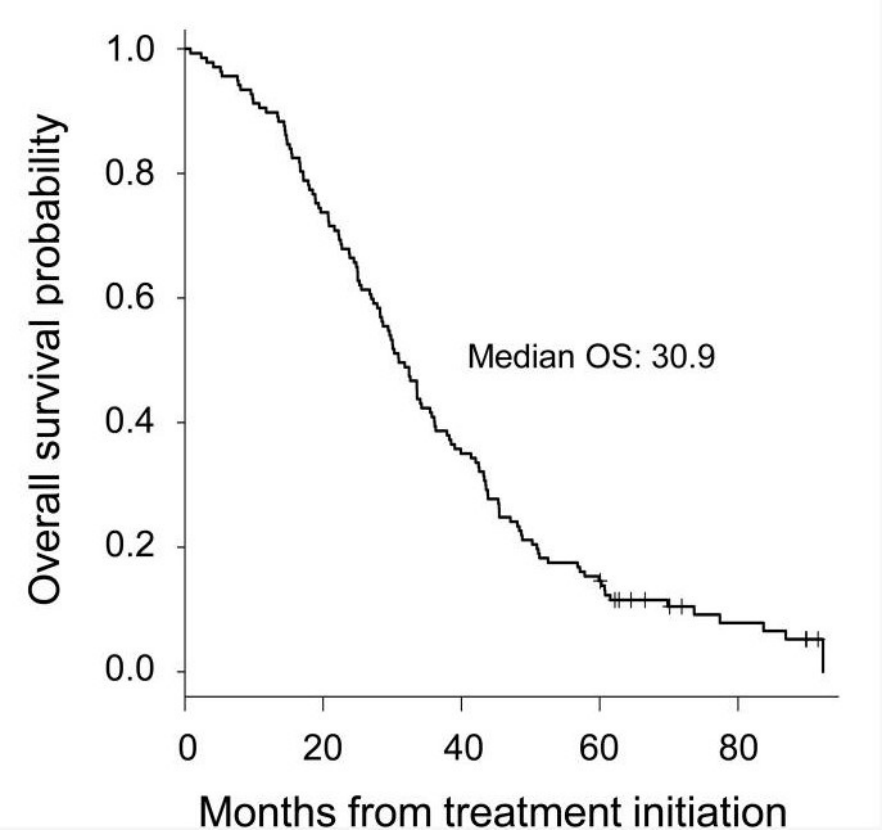
Medical doctor 2004 – had just finished as a GP.

Incarnated non-smoker.

Unfortunately 6 months later in february 2016 I was diagnosed with lungcancer (NSCLC) stage 3B, EGFR-mutated – at the age of 41y.

Progressed to stage 4 cancer in a half year (august 2016).

Kaplan-Meier-curve for *EGFR* mutated lungcancer



Lin, J. et al, JTO (2016)

Two stories on how to be met by the health care system in that situation:

- How we would like to have been met

- How we were met

How we would have liked to be met.

You have received a **very serious diagnosis**. Though of course everyone's case is unique and medical progress moves fast – **with the standard treatment that we offer today there's an average survival of just 30 months** – Here's some information on this.

Since the prognosis with standard care is so bad, we're **researching intensely to develop new treatments** that we hope will increase survival for the patients.

We're testing different experimental treatments.
Here's some information on some of those that we believe would be the most promising for you.
The treatments **are selected carefully by some of the world's leading researchers in this field**.

You must be aware that **most of the treatments will not have the effect we want**.
Therefore we will **follow you closely** to see if a treatment has an effect or not.
If it seems it is not working, **we will have other promising treatments** you can try out.

If you choose to do standard treatment that will of course also be ok.

Spend some time to go through this information and then we meet in a few days to decide which treatment we'll go for.

- ✓ **They have the same goal as us: I shall live as long as it is possible!**
- ✓ **They are competent**
- ✓ **They have a strong and well-thought through plan.**

How were we met?

What we did have (oral) information on:

- **Diagnosis**
- **Next step** – a PET scan...«so we'll see..«
- **Prognosis**: «maybe years..let's hope it has not spread... «
- «I know this old lady who comes in here every year just for her controls - amazing, it must be five years now I believe.. «
- «I'm very sorry...it's a very serious diagnosis..."try not to think too much."

We did not get any information on:

- **Possible treatment options** in case of a localized vs. a more advanced disease.
- High possibility for mutations and the possibility for targeted drugs.

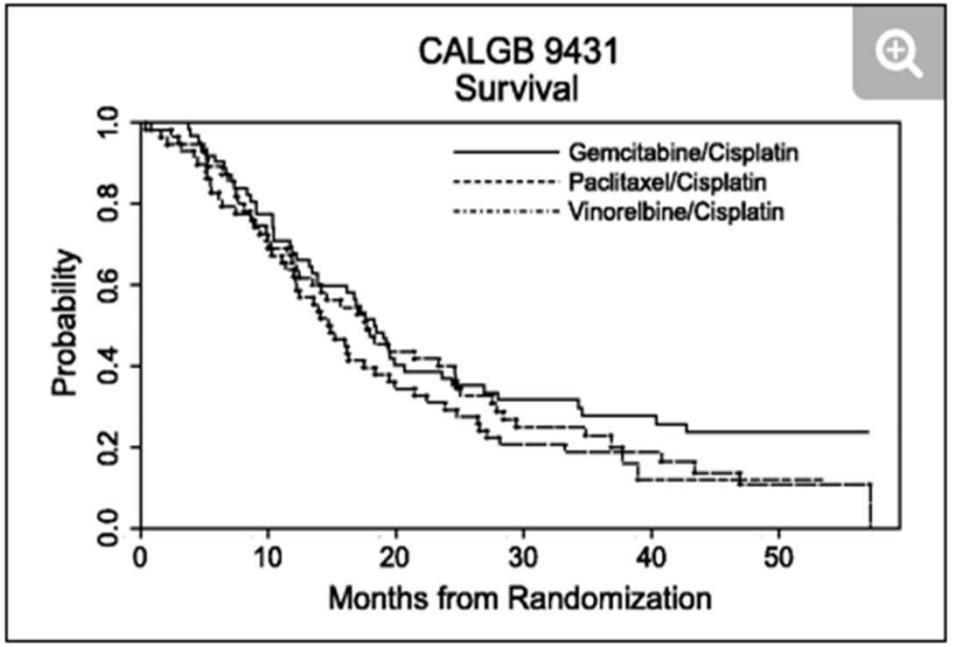
First reaction

We were spooked beyond words, so I started the offered treatment

- Chemo (Cisplatin+Vinorelbine) + radiation course were initiated – ”with curative intend”.
- For unresectable NSCLC stage3:

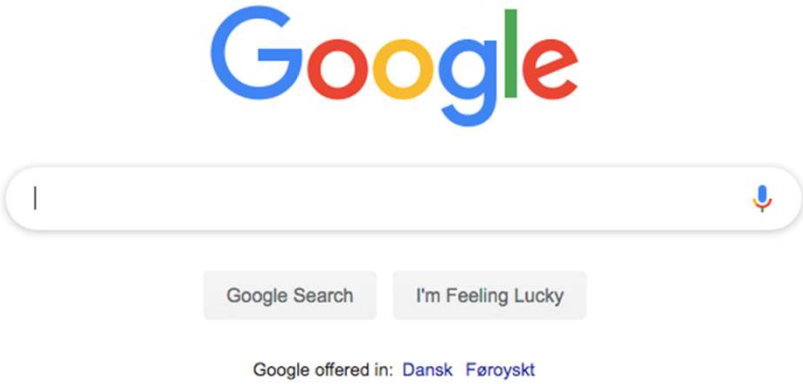
Table 2 Median Survival Range by Treatment Modality for Locally Advanced, Unresectable Stage III NSCLC (Phase 3 Trial Data)

Treatment Modality	Median Survival (Months)	3-Year Survival (%)
External beam radiation therapy alone (≥6000 cGy)	10-11[2,3]	<10
Sequential chemotherapy using high-dose cisplatin-based combination, then radiation	13-15[2-7]	10-20
Concurrent radiation and chemotherapy using high-dose cisplatin-based combination	12-17[4-7]	20-30
Concurrent chemoradiation → consolidation docetaxel	23-35[11,13]	30-40



Other reactions

- I started to google…
- I studied the research
- I came in contact with other patients



I started to understand:

If standard treatment leads to (almost) all patients dying after a short time, it does not seem wise just to follow standard treatment.

So I started asking questions...

Me	AUH
Can we add other treatment modalities to the treatment to make it work better?	No, nothing has been proved to work better.
Can I do something to make treatment work better? Diet, supplements..?	No, just don't loose weight.
What about after I end my treatment – anything we can do there?	No. Hopefully you will be cancerfree. Enjoy life.
Are there any trials I can be added to after I end my first line treatment?	No, we'll just wait and see.

I decided to do something more, so…

- When chemo/radiation was done, I asked for a ”restaging” - to find out if I was now considered operable. **I was**!
- I had a left lobectomy in june 2016 ”at my own risk”.
- Asking if some adjuvant treatment should be added

  (a targeted drug for a year, another round of chemotherapy or radiation,

  drugs during surgery..) – I was told: no - ”no evidence of this” (!).
- Unfortunately three months later in august 2016 relapse with 3 nodules in right lung + 1 lymph node – and after a board meeting it was decided that I was now **incurable stage 4**.
- Started oral drugs targeting my mutation (EGFR) =TKI/Tarceva.

Life as a stage 4 patient:

Follow standard treatment

Stay away from everything else

Wait & see…

Hope for the best.

No SBRT/ablation upfront for stage 4 patients on TKI ***(though it has been proven to work)***

Quite long intervals between scans ***(even in case of growth, because options are so sparse)***

No rutine MRI brain unless requested/symptoms ***(though 50% of NSCLC develop brain mets)***

No rutine PET scan unless requested

No additional testing of tumor tissue outside the standard package.

No ***(or regrettably few)*** **trials to participate in – and then only as "last option"**

The impression that gradually sunk in...

- The health care system was content as long as I followed the offered standard treatment...for as long as it could work....

  ”First do no harm”.

- I wanted to save my life.

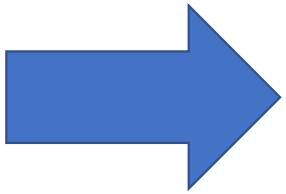
  ”No risk, no gain”.

- We had fundamentally different goals!

I was given up the day I was diagnosed with stage 4 cancer.

Unfortunately this is rutine

- I’m certainly not alone



It seems our health care system gives up rutinely on patients also young mothers and fathers, who get incurable (”terminal”) diagnoses.

There are done only few meaningfull attempts to save their lives.

Is this ok?

It is OK that you can not save the life of a (young) cancer patient.

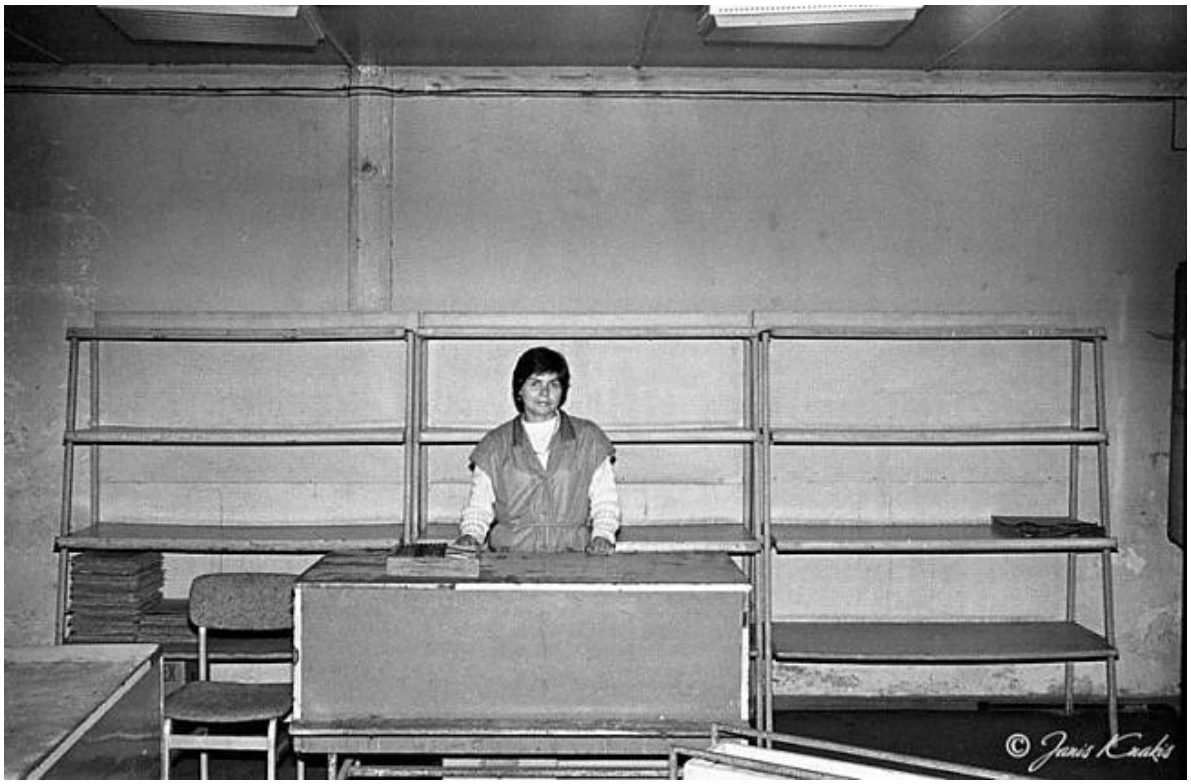
But there are no excuses for not trying the absolutely best!

Three suggestions to guidelines on how incurable/"terminally" ill (and maybe especially young) patients should be met:

1. Patients should be well and truthfully informed on their disease and the perspectives of the treatment initiated.
2. The health care system should have as a goal to save the lives of these patients.
3. The hospital should offer (or at least direct patients to) a variety of experimental treatments (within certain limits of course).

Unfortunately this is far from today's reality.

The offers to the incurable/”terminally” ill patients today:



- Few/no relevant clinical trials.
- No offered treatments with evidence level lower than phase 3.
- And to make it even worse:
  When patients bring initiatives of their own, they are mostly discouraged and warned – not guided or encouraged.

What do most patients with incurable/"terminal" diagnoses do, when they meet today's health care system?

- **Most cancer patients die after they have only received standard treatment**.
  - Double tragedy: patients die - and the health care system does not learn anything from it. They die in vain.

- **Many patients try out miscellaneous and sometimes even dubious alternative treatments on their own initiative**.
  - Health care system does not learn from their experiences.
  - Sometimes the health care system even refuses to follow/scan patients who are not accepting the recommended treatment.
- **Some patients seek treatments abroad**. Some with luck, some not
- **Only a small fraction of patients are enrolled in clinical studies during their disease course**:
  - 3% in USA
  - How many in Denmark?

What did I do - and what could I have done?

- I have received standard treatment
- After my stage 3B diagnosis I participated in one trial (NARLAL) using high dose radiation in combination with chemotherapy.

  I have not been offered any trials as a stage 4 patient.
  «

- I have added multiple treatments myself and are today without/almost without visible cancer.

BUT my disease situation could have been different and prognosis possibly better, IF I had only questioned many of the ”truths” I heard (or someone had pointed it out to me at the right time)...

Stage 4 incurable?

Targeted Oncology

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Driving Knowledge. Empowering Change. Optimizing

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Head & Neck Cancers
Hematology
HER2-Negative Breast Cancer
Immunotherapy
Liquid Biopsies
Lung Cancer
Lymphomas
Mantle Cell Lymphoma
Melanoma
MPNs
Multiple Myeloma
Ovarian Cancer
Prostate Cancer
Renal Cell Carcinoma
Skin Cancers
Thyroid Cancers

Publications > The Journal of Targeted Therapies in Cancer > 2018 > 2018 April >

Oligometastatic Disease in Cancer: Broadening the Path to Cure?

Joshua Bauml, MD; Charu Aggarwal, MD; Tracey L. Evans, MD; Christine Ciunci, MD, MSCE; Linda Miller, RN; Natisha Muhammad, MPH; Faith Mutale, CRNP; Christina Knepley, CRNP; Corey J. Langer, MD; and Ro
Published Online: Apr 27,2018

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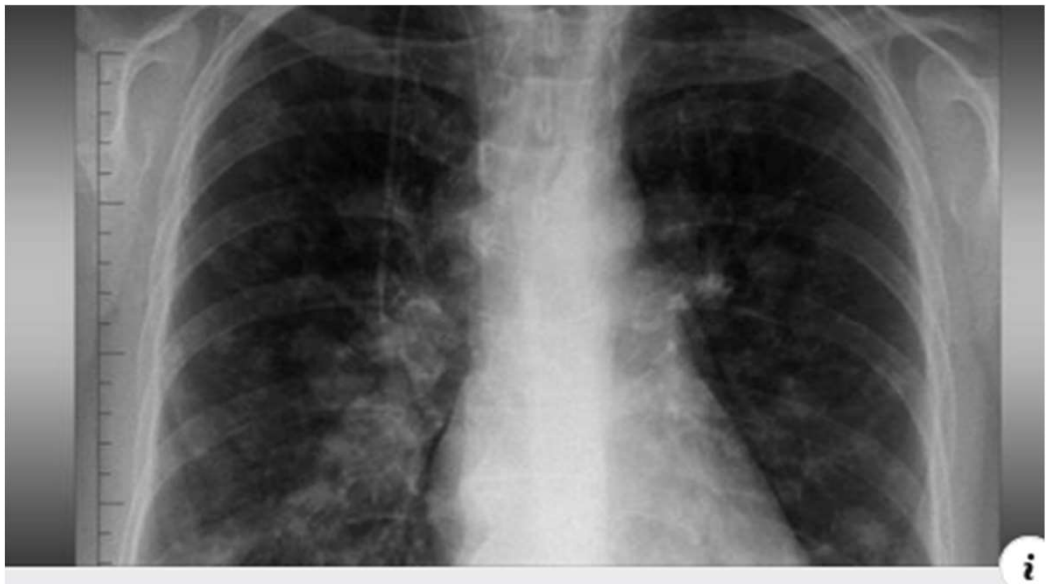
ABSTRACT

Joshua Bauml, MD

Emerging data indicate that patients with metastasis to a limited number of sites (termed oligometastatic disease) may have improved outcomes with the use of locally ablative therapy (LAT). In spite of limited, and at times, heterogeneous data, the availability of minimally invasive LAT has led to the widespread adoption of this practice for patients with oligometastatic disease. There are currently no clinical factors that are clear predictors of improved survival after LAT across tumor subtypes. New data suggest that the use of molecular biomarkers and combination therapies improve patient outcomes.



MEDSCAPE.COM

'Revolutionary': Some Oligometastatic Cancers Are Curable

Metastatic cancer has long been considered incurable. The concept of...

"The old paradigm of cancer metastases is, once cancer gets into [distant] lymph nodes or the blood vessels, there is no chance of cure," Bauml commented. Weichselbaum and Hellman showed that this paradigm is "not exactly accurate."

"We haven't really identified how to separate out those patients [who are curable], but just the concept that such a subgroup exists is really revolutionary."

Improving chemotherapy significantly…

Melatonin and Loratidin:

Melatonin could be an overlooked treatment for cancer

June 1, 2015 - 06:25

Cancer patients have a greater chance of survival if treated with the sleep hormone melatonin in addition to chemotherapy.

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By: Bo Christensen

Melatonin has been the

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Health - partner news

Over the course of one year, the chance of survival almost doubled from 28 per cent to 52 per cent, according to the study recently published in the Journal of the Danish Medical Association.

It might also have positive effects on our immune system and even slow the development of cancer cells.

Melatonin can do more than regulate our biological clocks. The natural sleep hormone can also slow the development of cancer cells and reduce the side effects of chemotherapy. (Photo: Colourbox)

Now, a meta study of melatonin and cancer research shows that the hormone is not only reducing the side effects of chemotherapy but might also be effective at eliminating cancer cells.

Over the course of one year, the chance of survival almost doubled from 28 per cent to 52 per cent, according to the study recently published in the Journal of the Danish Medical Association.

of Science and Techno

C-sections by trained officers a safe alterna

News from Gemini, NT Trondheim - Norwegiar of Science and Techno

Tick-borne encephalit found in unpasteurize in Norway

News from The Norwe Veterinary Institute

Health personnel stru interacting with patie suicidal thoughts

News from Inland Nor University of Applied S INN University

EBioMedicine. 2016 Jul; 9: 130–139.
Published online 2016 Jun 7. doi: 10.1016/j.ebiom.2016.06.013
PMCID: PMC4972561
PMID: 27333030

Repurposing Cationic Amphiphilic Antihistamines for Cancer Treatment

Anne-Marie Ellegaard,[a] Christian Dehlendorff,[b] Anna C. Vind,[c] Atul Anand,[a] Luise Cederkvist,[b] Nikolaj H.T. Petersen,[a,1] Jesper Nylandsted,[a] Jan Stenvang,[c] Anders Mellemgaard,[d] Kell Østerlind,[e] Søren Friis,[b] and Marja Jäättelä[a,*]

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This article has been cited by other articles in PMC.

Associated Data

Supplementary Materials

Abstract

Go to:

Non-small cell lung cancer (NSCLC) is one of the deadliest cancers worldwide. In search for new NSCLC treatment options, we screened a cationic amphiphilic drug (CAD) library for cytotoxicity against NSCLC cells and identified several CAD antihistamines as inducers of lysosomal cell death. We then performed a cohort study on the effect of CAD antihistamine use on mortality of patients diagnosed with non-localized cancer in Denmark between 1995 and 2011. The use of the most commonly prescribed CAD antihistamine,

Patients, who had chemotherapy and took Loratidin at the same time, had a 24% lower risk of dying compared to patients who did not take this drug.

Improving chemotherapy significantly…

Fasting and alkaline diet:

Science/Technology

Fasting-like diet turns the immune system against cancer

A low-calorie fasting-like diet, plus chemotherapy, enables the immune system to recognize and kill skin and breast cancer cells, according to a new USC-led study on mice

They also found three cycles of the fasting diet, combined with doxorubicin, prompted a 33 percent increase in the levels of cancer-fighting white blood cells and doubled the number of progenitor cells in the bone marrow. The cancer-killing cells were also more effective at attacking and shrinking the tumors.

The scientists found that short-term starvation (a two-day, water-only diet) and the low-calorie fasting-like diet in mice reduced the expression of the HO-1 gene in the T regulatory cells. This change made it easier for the chemotherapy drugs to attack the cancer.

How might baking soda boost cancer therapy?

Researchers describe how acidity turns oxygen-starved cancer cells dormant and drug resistant -- and a potentially easy way reverse the effect

Date: June 1, 2018

Source: Ludwig Institute for Cancer Research

Summary: A new study has uncovered an entirely novel mechanism by which cells enter a state of dormancy as tissues starved of oxygen become increasingly acidic.

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RELATED TOPICS

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FULL STORY

A Ludwig Cancer Research study has uncovered an entirely novel mechanism by which cells enter a state of dormancy as tissues starved of oxygen become increasingly acidic. The study, led by Chi Van Dang, scientific director of the Ludwig Institute for Cancer Research, has potentially significant implications for cancer therapy: Large swaths of solid tumors are often deprived of oxygen, and cells in such patches are thought to be a major source of drug resistance and disease relapses.

SUMMARY

Recent reports indicate that hypoxia influences the circadian clock through the transcriptional activities of hypoxia-inducible factors (HIFs) at clock genes. Unexpectedly, we uncover a profound disruption of the circadian clock and diurnal transcriptome when hypoxic cells are permitted to acidify to recapitulate the tumor microenvironment. Buffering against acidification or inhibiting lactic acid production fully rescues circadian oscillation. Acidification of several human and murine cell lines, as well as primary murine T cells, suppresses mechanistic target of rapamycin complex 1 (mTORC1) signaling, a key regulator of translation in response to metabolic status. We find that acid drives peripheral redistribution of normally perinuclear lysosomes away from perinuclear RHEB, thereby inhibiting the activity of lysosome-bound mTOR. Restoring mTORC1 signaling and the translation it governs rescues clock oscillation. Our findings thus reveal a model in which acid produced during the cellular metabolic response to hypoxia suppresses the circadian clock through diminished translation of clock constituents.

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Anticancer Res. 2017 Sep;37(9):5141-5145.

Effects of an Alkaline Diet on EGFR-TKI Therapy in EGFR Mutation-positive NSCLC.

Hamaguchi R[1], Okamoto T[2], Sato M[3], Hasegawa M[3], Wada H[3].

Author information

Abstract

BACKGROUND: The acidic tumor microenvironment is associated with progression of cancers. The purpose of this study was to investigate the association between an alkaline diet and the effect of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) in non-small cell lung cancer (NSCLC) patients.

PATIENTS AND METHODS: Eleven advanced or recurrent NSCLC patients with EGFR mutations treated with EGFR-TKI after being instructed to follow an alkaline diet were retrospectively evaluated.

RESULTS: The median progression-free survival (PFS) and overall survival (OS) were 19.5 (range=3.1-33.8) and 28.5 (range=15.4-46.6) months. The average dosage of EGFR-TKI was 56±22% of the standard dosage. Urine pH was significantly increased after the alkaline diet (6.00±0.38 vs. 6.95±0.55; p<0.05).

CONCLUSION: An alkaline diet may enhance the effect of EGFR-TKI treatment in NSCLC patients with EGFR mutations.

KEYWORDS: EGFR mutation; Na+/H+ exchanger; Non-small cell lung cancer; alkaline diet; fruit and vegetables; low dose EGFR-TKI; pH regulation; tumor microenvironment; urine pH

PMID: 28870946 DOI: 10.21873/anticanres.11934

diet. The progression-free survival (median=19.5 months) and overall survival (median=28.5 months) of this group was longer than that reported in publications of the similar population treated with EGFR-TKI alone (median progression-free survival=9.2-13.3 months, median overall survival=18.6-22.8 months) (14-18). EGFR-TKI therapy has prolonged

Etodolac and Propranolol in relation to surgery can probably reduce risk of relapse after cancer surgery significantly – *so why is this not tried?:*

The ASCO Post

ABOUT NEWS MEETINGS TOPICS VIDEOS

Perioperative Anti-inflammatory, Antistress Drugs May Reduce Postsurgical Metastatic Disease Recurrence

By The ASCO Post
Posted: 8/7/2017 10:23:38 AM
Last Updated: 8/7/2017 10:23:38 AM

Key Points

- 38 patients with breast cancer were given a pharmacologic treatment—a beta blocker, propranolol hydrochloride, and a nonsteroidal anti-inflammatory drug, etodolac—5 days before their surgeries, the day of their surgeries, and 5 days after their surgeries.
- The drugs were very efficient in reducing biomarkers of metastatic processes.
- The drug treatment reversed epithelial–mesenchymal transition and was able to improve immune competence and reduce inflammation.

Most cancer-related deaths are the result of postsurgical metastatic recurrence. A new Tel Aviv University (TAU) study published by Shaashua et al in *Clinical Cancer Research* found a specific drug regimen administered prior to and after surgery significantly reduces the risk of postsurgical cancer recurrence. These medications, a combination of a beta blocker and an anti-inflammatory agent, may also improve the long-term survival rates of patients. The treatment is safe, inexpensive (two medications similar in price to aspirin), and easily administered to patients without contraindications.

Unconventional Approach

"We've taken an unconventional approach, deviating from the current medical dogma that refrains from intervening during the short period surrounding a cancer surgery—no chemo[therapy], radio[therapy], or immune therapy for at least 3 weeks before or after surgery," said senior study author **Shamgar Ben-Eliyahu, PhD**, of TAU's School

Study Findings

For the study, 38 patients with breast cancer at Sheba Medical Center, Kaplan Medical Center, and Rabin Medical Center were given a pharmacologic treatment—the beta blocker propranolol hydrochloride (used to reduce blood pressure and anxiety) and a nonsteroidal anti-inflammatory drug, etodolac (used to reduce inflammation)—5 days before their surgeries, the day of their surgeries, and 5 days after their surgeries. Blood and tumor tissue samples were then analyzed using whole-genome gene-expression profiling to identify all the RNAs expressed in malignant cells and leukocytes.

"We found that the drugs were very efficient in reducing biomarkers of metastatic processes," Dr. Ben-Eliyahu said. "For example, we found that the drug treatment reverses epithelial–mesenchymal transition—the process that tumor cells go through to slip out of the primary tumor and enter another organ. It is a crucially important step in the metastatic process. We also looked at indices related to the immune system and were able to improve immune competence and reduce inflammation with the drugs."

The research team has conducted a similar study, which has not yet been published, in patients with colorectal cancer and has found similar results.

The researchers are currently considering a larger-scale clinical trial to establish the clinical long-term beneficial effects of this treatment. "Positive outcomes should validate this treatment and lead to its becoming available for most cancer patients," Dr. Ben-Eliyahu concluded.

The content in this post has not been reviewed by the American Society of Clinical Oncology, Inc. (ASCO®) and does not necessarily reflect the ideas and opinions of ASCO®.

Targeted therapy (TKI) after surgery might have prolonged my recurrence free interval

- so why was I not offered this?

Improved Disease-Free Survival With Adjuvant Erlotinib in *EGFR*-Mutant, Early-Stage NSCLC

Susan Moench, PhD, PA-C

In the open-label, single arm, phase 2 SELECT (Surgically Resected EGFR-Mutant Lung Cancer With Adjuvant Erlotinib Cancer Treatment) study of adjuvant erlotinib following adjuvant chemotherapy with or without radiation therapy in patients with resected early-stage, *EGFR*-mutant non-small cell lung cancer (NSCLC), individuals showed improved 2-year disease-free survival (DFS) compared with genotype-matched historical controls. The trial results were published in the *Journal of Clinical Oncology*.[1]

Individuals with early-stage EGFR-mutant NSCLC who were administered erlotinib showed improved 2-year DFS compared with genotype-matched historical controls.

Study-eligible patients had stage IA to IIIA NSCLC characterized by an activating *EGFR* mutation, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 2, and had undergone surgical

Different ordinary drugs can be **repurposed** as drugs against cancer – inhibiting cancer at a basic metabolic level - to make standard treatment work better - *three examples*

- **Metformin** (oral diabetes drug) – can if added to ordinary standard treatment (TKI), increase OS from 19 to 27.2 months in NSCLC. (Price: 10$/month).


ASCO Meeting Library

Combination of metformin plus TKI vs. TKI alone in EGFR(+) LUNG adenocarcinoma: A randomized phase II study.

Presented Sunday, June 3, 2018

Abstract Poster

Authors:

Oscar Gerardo Arrieta Rodriguez, Feliciano Barron Barron, Miguel-Ángel Salinas Padilla, Laura Alejandra Ramirez-Tirado, Diana Flores-Estrada, Graciela Cruz-Rico, Manuel Jesús Arguelles Jiménez, Andres Felipe Cardona Zorrilla; Instituto Nacional de Cancerologia (INCan), Mexico City, Mexico; Instituto Nacional de Cancerología (INCan), Mexico City, Mexico; Instituto Nacional de...

Methods:

In this phase 2 clinical trial (NCT03071705) we randomly assigned 116 patients with stage IV *EGFR*-mutated lung adenocarcinoma to receive therapy with metformin + EGFR-TKI (M+TKI) (n = 49) or EGFR-TKI (TKI) alone (n = 67). TKI was chosen upon clinician´s discretion. Patients were excluded if they had a history of diabetes or had received therapy with metformin or TKIs (> 2 cycles) previous to enrollment. The primary endpoint was PFS, secondary endpoints included objective response rate (ORR), disease control rate (DCR) and OS.

Results:

Baseline characteristics were well balanced between treatment arms. Mean patient follow up was 12.9 (±10.9) months. Median PFS was significantly longer for patients receiving M+TKI compared to those who received TKI (14.0 months vs. 10.0 months; p = 0.017) . ORR was higher in the experimental arm of the trial, compared to the control group (67.4% vs. 47.5%; p = 0.044), although, the DCR was similar in the two groups (97% vs. 88.5%; p = 0.085). Median OS was 24.8 months. Patients receiving M+TKI had a longer OS compared to those receiving TKI (27.2 months vs. 19.0 months, p = 0.015). Multivariate analysis showed that, among others, the therapeutic arm (M+TKI vs. TKI) is an independently associated factor for both PFS and OS.

- **Itraconazol** (oral antifungal drug) in combination with Pemetrexed **quadrupled** (x4!) survival from 8 to 32 months in lung cancer
  - *why are not all lung cancer patient offered this?*

Phase 2 Study of Pemetrexed and Itraconazole as Second-Line Therapy for Metastatic Non-Squamous Non-Small Cell Lung Cancer

Charles M. Rudin, MD, PhD, Julie R. Brahmer, MD, Rosalyn A. Juergens, MD, PhD, Christine L. Hann, MD, PhD, David S. Ettinger, MD, Rosa Sebree, BS, Ruth Smith, RN, Blake T. Aftab, PhD, Peng Huang, PhD, and Jun O. Liu, PhD

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Abstract

Purpose

Preclinical studies suggested tha
migration, and tube formation of
enhances the efficacy of cytotox
on these data, we performed an
cytotoxic chemotherapy in the tr

Patients/Methods

The study enrolled patients with
cytotoxic therapy for metastatic
without itraconazole 200 mg ora
progression-free at 3 months, pr

Results

A total of 23 patients were enrolled; the study was stopped early due to increasing use of pemetrexed in the first line setting. Sixty-seven percent of patients were progression-free at 3 months on itraconazole plus pemetrexed vs. 29% on the control arm of pemetrexed alone (p=0.11). Median progression-free survivals were 5.5 months (itraconazole) vs. 2.8 months (control) (hazard ratio (HR)=0.399, p=0.089). Overall survival was longer in patients receiving itraconazole (median 32 months) vs. control (8 months) (HR=0.194, p=0.012). There were no evident differences in toxicity between the study arms.

Conclusion

Itraconazole is well tolerated in combination with pemetrexed. Consistent with our preclinical data, daily itraconazole administration is associated with trends suggestive of improved disease control in patients receiving chemotherapy for advanced lung cancer.

Keywords: Itraconazole, anti-angiogenic, lung cancer

- **Tetrathiomolybdate** (oral copper chelator) is a very powerful inhibitor of metastatic disease, inhibiting establishment of new growth in high risk patients.

Set-up: 75 women TNBC stage 2,3&4 - All NED.

After 7.1 years: 59.3% of TNBC stage 4 patients still **CANCERFREE** (83% for TNBC stage 2&3)

No mentionable side effects.

Abstract P1-10-02: A phase II study of copper-depletion using tetrathiomolybdate in patients with breast cancer at high risk for recurrence: Updated results

S Sahota, A Willis, N Kornhauser, M Ward, M Cobham, T Cigler, A Moore, E Andreopoulou, V Fitzpatrick, S Schneider, N Prima, A Wiener, D Ko, A De Laurentiis, JD Warg, A Rubinchik, V Mittal, ar

DOI: 10.1158/1538-744

Article Info

Abstracts: 2017 San

Abstract

Background: Metal cancer and anti-met catalytic cofactor in carcinogenesis. Am (EPCs) and copper- hypothesized tetrath by reducing the num niche. These results

Methods: A single arm phase II study of breast cancer (BC) patients (pts) at high risk for recurrence, defined as node+ triple negative (TNBC), stage 3 and 4 with no evidence of disease (NED) were enrolled on a trial of CD with TM. TM was given to maintain ceruloplasmin (Cp) levels between 8-16 mg/dl for two years with an extension phase or until relapse. The primary endpoint was a change in EPCs measured by flow cytometry before and during treatment. Secondary endpoints included tolerability, safety, PFS and LOXL-2 levels.

Results: Seventy-five pts received 2778 cycles of TM on the primary and extension study. The primary study treatment duration was 24 cycles (each cycle is 28 days) plus an extension phase. The median age is 51 years (range 29-66). Forty-five pts have stage 2/3 BC and 30 with stage 4 NED. Forty-eight percent of pts are TNBC and 40% of pts are stage 4 NED. Median Cp levels were monitored with each cycle. A decrease from 28 to 16 ($p<0.0001$) was seen after one cycle. Interestingly, TNBC pts seemed to have a greater decrease from 23.5 to 13 after one cycle. TM was well tolerated with grade 3/4 toxicities including: reversible neutropenia (2.3%), febrile neutropenia (0.04%), fatigue (0.2%). Five-year analysis showed a decrease in EPC's ($p=0.004$) and LOXL-2 ($p<0.001$). At a median follow-up of 7.1 years, the EFS for 75 pts is 71.4%. The EFS for 36 pts with TNBC is 71.7%. EFS for stage 2/3 TNBC is 83% and for stage IV TNBC is 59.3%.

Conclusions: TM is safe, well tolerated and appears to affect multiple components of the tumor microenvironment that have been identified in pre-clinical models as important for progression.

So what have I done so far?

- **Researching**, attending **conferences**, **consulting** international top specialists/doctors and researchers in the field of NSCLC and of immunotherapy - and **engaging in international patient groups** of mostly young progressive NSCLC patients and caregivers with the same goals as me.
- Choosing/alternating **diet** (at moment lowglycemic/anti inflammatory)
- Added several **repurposed drugs** with wellproven scientific effect against cancer (many phase 2 studies): Tetrathiomolybdate, Metformin, Simvastatin, Mebendazol, Doxycykline, Dipyridamole (Persantin) and Loratidin.
- Added several **supplements** with same scientific evidence (zinc, Berberine, D3 etc)
- **Personalized peptide vaccine** made in Germany, based on the results of a sequencing of my tumor.
- I have managed to find an **oncologist** who is interested, to some extent adventurous and supports me in the above - even though he might not think it will work.
- Looking into: **intratumoral injections** (in situ vaccines), **oncolytic therapy**, new promising **combination treatments** - and a repurposed drugs database.

Why is it so?

Lack of goal and incentive in the health care system

- Pointless/in vain to initiate (e.g. local) treatment in stage 4 patients?
- ”First do no harm”: ”we don’t want to add something that we don’t know if you will benefit from” and ”we don’t want to harm you”.

Lack of coordination with the patients wishes

– e.g. younger patients will might be willing to take higher risks to achieve higher goals.

A chance of a cure/significantly prolonged life - by taking some well calculated risks - can be much more attractive than just ”a few good years”.

Lack of flexibility in the health care system

– No ”Right to try”

– Need for phase 3 evidence for treatments to get implemented/tried out.

What can we do? *In my opinion we need to…*

Rethink our trial system:

- Branch it out significantly, so that in the future 97% of all cancer patiens will participate in trials during their disease course (and not just 3%).
- Be much bolder in combining treatments (combining only 2 treatments is unambitous – *does anybody really think it will work?)*
- **Accept less that phase 3 level of evidence** where good phase 2 evidence is present.

Searching for phase 3 evidence is expensive, time consuming, delays the use of good treatments - and for some treatments (e.g. repurposed drugs) not even realistic to do phase 3 studies).

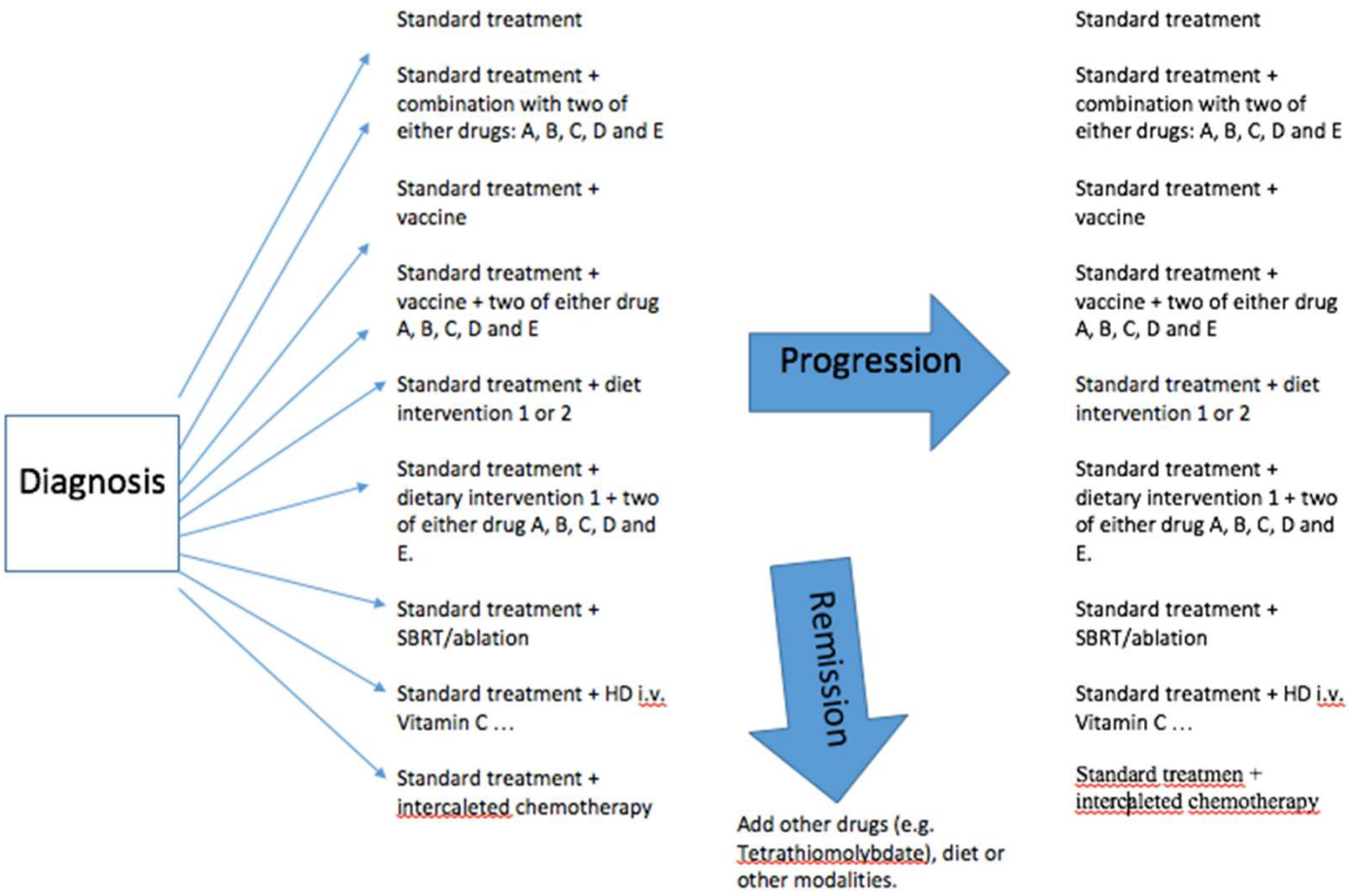
Gather big amounts of knowledge/information/ experience in a short time

Speed up research for better treatments (a cure?)

Prolong the survival for patients here and now.

We need ”**a right to try**”

It could look something like this:



Could it work?

Yes I believe so!

In fact it has already been done.

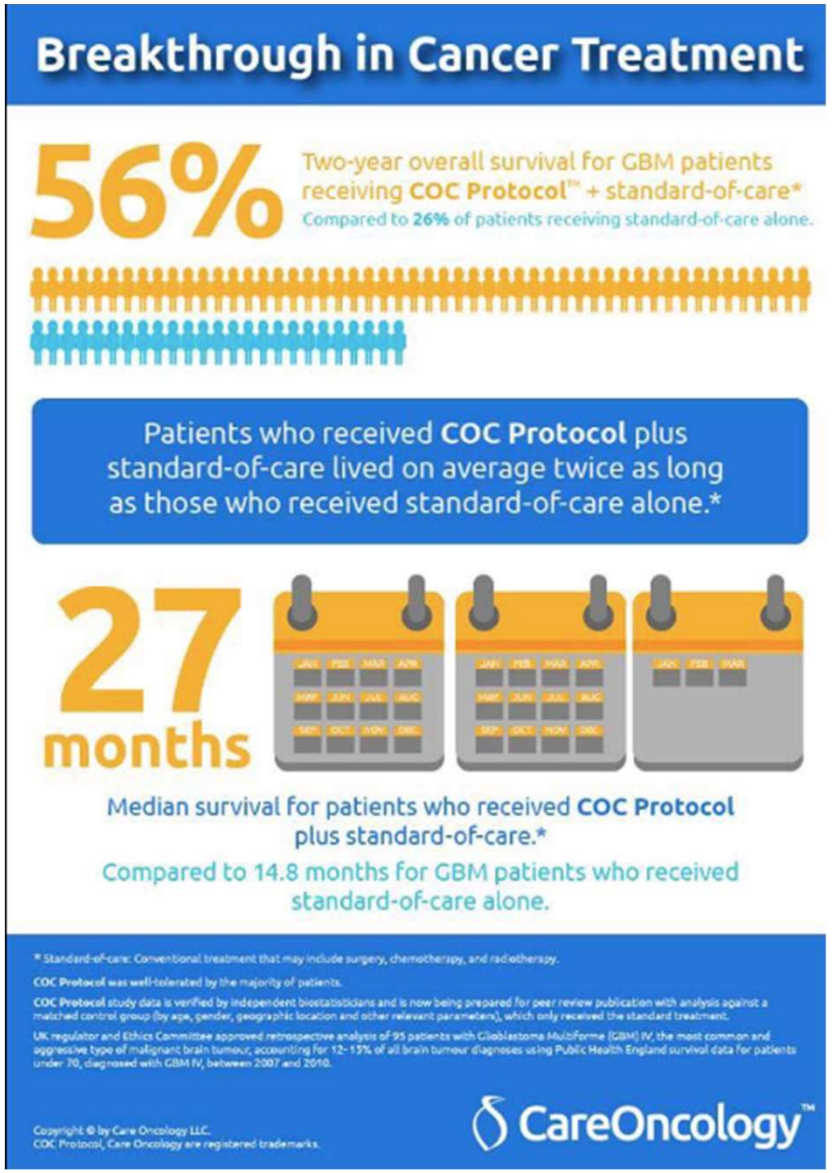
Standard treatment in combination with the four ordinary (”repurposed”) drugs:

Metformin, Atorvastin, Mebendazole and Doxycykline

has almost doubled survival in stage IV patients.

This trial has been carried out by Care Oncology Clinic in London.

Now imagine what adding SBRT, vaccines and other drugs like Tetrathiomolybdate could do to these numbers.



Summary

- Yes, we can do this!
- To me it seem unethical not to take advantage of the knowledge already available to try and prolong life significantly for incurable patients.
- If we keep repeating what we have always done, we will end up in the same place.
- We need to rethink and expand the clinical trial system dramatically to speed up the process of transforming stage 4 cancer into a chronic or even curable disease.

Thank you for your attention!

Inspirational documentaries/books:

How to survive a plague:
www.surviveaplague.com
Surviving Terminal Cancer:
www.survivingterminalcancer.com
Curing Cancer with Immunotherapy:
www.curingcancerbook.com