im excited to introduce todays lecture

recognized expert in immunotherapy for

cancer

he serves as the chief of the gu

malignancy branch within the center for

cancer research of the national cancer

institutes national institutes of

health hes also the director of medical

oncology services

in addition he heads the immunotherapy

section within the ccr

dr gully received his md phd from loma

linda university and completed his

internal medicine residency at emory

university please enjoy the presentation

im james gulley im chief of the

genital urinary malignancies branch and

director of the medical oncology service

here at the national cancer institute

but my academic interest is

immunotherapy and today were going to

be talking about the

pharmacology of immunotherapy

as an immunologist i think about cancer

in a simple way i think that there are

tcell inflamed tumors as you can see

over here on the

right and t cell poor tumors depicted

here on the left

these t cell inflamed tumors can be t

cell inflamed because the immune system

recognizes the cancer often because

there are viral associated targets

within the cancer or there are mutations

and these can make

neo antigens

a very interesting recent review was

done looking at the body of data on

immune infiltrates within cancer

and the responses to treatment and

patient outcomes

and there were references in

different diseases

that were showing

improved outcomes based on the immune

infiltrate within the tumor

so in order to understand whats going

on i think its

important to understand the interaction

between the t cell which is the main

immune cell well be talking about today

and the tumor a t cell can recognize the

tumor when the t cell receptor

binds to the anagen mhc complex

either in the tumor or in the antigen

presenting cell that t cell then

can if its specific for that antigen

mhc complex can become activated and can

kill the cell it can either kill via

ligating fast ligand thats present on

the tumor cell or via releasing

granzymes and perforin that can lyse the

tumor cell

however

often there are multiple negative

regulatory influences within the tumor

microenvironment such as regulatory

cells like t regulatory cells depicted

here

or milo derived suppressor cells theres

also often

ido tgf beta or il0 that can shut down

an immune response and

there are

pd and pdl

can shut down a tcell response in

addition

and well talk more about that in just a

minute

today were going to be talking about

three different types of immunotherapy

about

the t cell checkpoint modulation

about

t cell adoptive transfer and about t

cell

or sorry therapeutic cancer vaccines

because of time well not be spending a

lot of time talking about the antibody

drug

conjugates lets

first talk about t cell checkpoint

modulation

there are really three different signals

for t cell activation the first signal

we we talked about already

when you have a t cell receptor that

binds to the mhc

peptide complex

in a normal cell

you see

that there is no second signal there is

no costimulatory

molecules on the pres on the surface of

the normal cell and so this

doesnt lead to activation of a t cell

however

antigen presenting cells such as

dendritic cells shown here

have this second

signal this costimulatory molecule they

can bind to its ligand on the t cell and

cause activation of that t cell in

addition dendritic cells can cause

further activation by releasing

cytokines that that

stimulate the t cell further

so lets talk now about the the

checkpoint modulation

what happens

um

is that there are

checkpoints that shut down

a t cell response

so you have these positive

costimulatory molecules and you have

negative costimulatory molecules and

these negative costimulatory molecules

will shut off a t cell response

and so if you have an antibody that

breaks that interaction you can allow

for continual activation of that t cell

and well talk about that in a little

bit but there are multiple different t

cell

markers were going to focus on pdl

ctla and pd

so first lets talk about ctla

ctla is upregulated shortly after

t cell activation

and you can see here

in this activated t cell up regulation

of of ctla and what this does is it

actually shuts the t cell back off so

theres this balancing act where if you

get activation the immune system tries

to bring it back to

no activation so that there isnt a

hyper activation

turns out that

that mice that have ctla

knocked out

will die

soon after birth because of massive

lymphoid infiltrates within their organs

epilimumab the

human antictla antibody

was approved for the treatment of

metastatic melanoma in 00 and it was

based in part on this study and one

other study where there was an

improvement in overall survival scene

and you can see here that

the proportion of of patients having

twoyear

survival was 0

at the 0 milligram per kilogram dose

level and comparing that with the

standard of care at the time tamidar

you saw the

year survival

so what cells are

does this epilimumab effect well it

turns out as we discussed it does affect

the

t activated effector t cells and you can

see here in the upper panel that

you have

a t cell once it gets activated will

upregulate the ctla and that will tend

to down regulate that but if you have

antictla binding to that that negates

that negative signal and you you can

allow that t cell to remain activated

in addition

t regulatory cells these cells that try

and shut down an immune response it

turns out that they have ctla thats

constitutively

present on the surface of those cells

in this case ctla

antibodies could lead to depletion of

those cells and that has been shown in

animal uh studies however it has not yet

been shown in humans

now i want to switch gears and talk

about pd and pdl

the pd typically is found on the

tcell and the pdl its ligand program

death ligand one is found on the tumor

cells it turns out when you have that

activated t cell

you will

you can have that t cell start to fight

the tumor and that

and

it does so in part by

releasing immune mediators such as gamma

interferon what happens with gamma

interferon is theres up regulation of

pdl expression on the tumor cell and

all of a sudden youre in checkmate here

with the the t cell cant

do its function it gets shut down and

the tumor cell is still alive however if

you come in with an antibody to pd or

pdl break that

you can allow that t cell to remain

fully functional fully reactivated and

can lead to death of the tumor cell

and indeed weve seen

significant activity with multiple

different pd and pdl inhibitors

across a wide range of different tumors

weve seen rapid deep and durable

responses

however

i would argue that weve only seen this

in a subset of patients not everybody

responds and well talk a little bit

about that

but based in part on the data that you

saw

the fda approved

both nivolumab and pembrolizumab

initially for melanoma in 0 and then

as you can see for a variety of

different indications and the list

continues to grow

each

month

and well talk a little bit about a very

interesting indication with msi high

tumors that was recently approved

both nivolumab and pembrolizumab have a

similar side effect profile and similar

level of clinical activities however

there have not been headtohead studies

at this point

theyve also been more recently

fdaapproved antipdl antibodies

atyzalizumab avilumab and dervalumab

are all approved and again they have a

similar side effect profile similar

level of clinical activity and really

the

one difference between these three is

that while they are all igg

antibodies only available is capable of

mediating adcc

so what is adcc or antibody dependent

cellular cytotoxicity well talk a

little bit more about that in the next

slide but

basically its another way that the

immune system can kill cells

so

one of the issues is that pdl can also

be present on some activated t cells and

the

um both atiszalizmab and dervalumab were

actually changed so that they wouldnt

mediate adccc

however

in

patients treated with a velomab

and in preclinical studies with a

velumab it was shown that there was

substantial adcc in the tumor but not in

the peripheral blood mononuclear cells

and in patients treated there was no

decrease in pdl subsets

so in addition to having another shot on

goal perhaps this

were going to see the

best

evidence of

the activity of adcc when we use it in

combination with other therapies that

that help increase nk cells because what

happens with adcc is that if the

antibody binds to the tumor

you can have nk cells that will bind to

that bound antibody and and cause

killing

so you could have not only the t cell

involved but the natural killer cell

involved also

this is an example of a patient treated

here at the national cancer institute

with avila mab

this patient had merkel cell carcinoma

and you can see

a very disfiguring

mass of lesions

on his neck he had a very nice response

and indeed biopsy

showed that there was a complete

response here and the patient

continues on study here

many months later

in merkel cell carcinoma which available

was approved for

you can see standard of care therapy

gives you this

progressionfree survival with

very few patients

and no patients actually being

progression free at one year however

with a villumab heres your progression

free survival rate and you can see that

in those patients that

that respond you have a very prolonged

progressionfree survival compared to

what is expected in this disease state

and based in part on this data

the fda approved

a villamab for merkel cell carcinoma

and this is another example this is a

pembrolizumab

and this is data in urothelial

cancer bladder cancer

you can see here that this was compared

with chemotherapy and that the median

survival was improved there

but the progressionfree survival was

not improved

the median progressionfree survival was

not improved although there was a tail

on the curve as you can see in the lower

panel

interestingly and this is something

were going to come back to there were

fewer treatment related adverse events

of any grade in the pembrolizumab group

versus the chemotherapy group

i want to touch on one thing here and

that is the likelihood of response to

the pd and pdl inhibitors

it turns out that

many of the cancers for which

these checkpoint inhibitors have been

approved are cancers that have higher

mutation burdens as you can see on the

right hand

side of the screen

these include melanoma lung cancer

bladder cancer etc

but i would argue its not just those

tumors but its really the mutation

burden itself and there was a very

interesting recent approval

based on

microsatellite instability and those

patients who have microsatellite

unstable tumors

those patients

tend to respond quite well and

pembrolizumab was recently approved for

microsatellite instability high tumors

irrespective of the histology and this

is the first histology agnostic

approval

by the fda

but i would also argue that

those

patients that have the higher mutation

burden those are the probably the t cell

inflamed tumors as we talked about at

the very beginning and they probably

have the neoantigens whereas the the

tumors that have lower mutation burdens

those are tcell pore tumors

and you may need to

target

something else

to get that immune system going you may

need to get a vaccine to do that

and so there are two approved

therapeutic vaccines for cancer cepulus

lt which was approved in 00 and was

the first modern era immunotherapy drug

to be approved

and

the tvec or telemogene

was approved for melanoma in 0

so lets talk a little bit about sepulus

lt

sapola cell t

um

is a vaccine before we do that lets

talk a little bit about the

the immunogenic versus nonimmunogenic

tumors so if you have an immunogenic

tumor all you would need potentially is

an immune checkpoint inhibitor to

unleash those immune cells that are

already there

but with a nonimmunogenic tumor you

need something else such as a

vaccine

and

to really have most effective immune

responses i think you need to

both

generate an immune response or if one is

already present thats fine but then

allow those immune cells to be effective

within the tumor microenvironment and

well come back to that in a minute so

lets talk then about

therapeutic vaccines

so there are a variety of different

therapeutic vaccines that are currently

under development right now

when one is looking at therapeutic

vaccines one needs to

select the appropriate antigens and

there are

programs out there looking at

tissue lineage antigens or antigens that

are overexpressed in in tumors and there

are also programs out there looking at

neoantigens

that are found specifically only in the

tumor

there you also need to

bear in mind the different types of

adjuvant that you might need to use with

this and the different ways of getting

that antigen to the to the immune system

and these could be either by a vector

via pulsing dendritic cells or via

bacterial vector or viral vector

so lets talk about an antigen

presenting cellbased vaccine

and that is the

sepulus lt or provenge this was the very

first approved

vaccine

therapeutic vaccine for cancer and this

was approved in 00

patients undergo leukopheresis where

there is removal of whole blood

that is sent through a machine where

that takes out the white blood cells and

gives the patient back everything else

and then those white blood cells are

sent to a central processing facility

where those

antigen presenting cells part of the

white cells are enriched for by density

sensor centrifugation

and pulsed with a p prosthetic acid

phosphatase a gmcsf fusion protein

and this

then is

analyzed then is sent back to the

physicians office where this product

can be infused into patients this whole

process takes about three days

and it is repeated three times over the

period of about one month

there was a large randomized phase three

study that led to the approval of

sepuloc lt and this showed a improvement

in median overall survival about a

percent or 0

improvement in

the risk of death and a four and a half

month

month rather improvement in median

overall survival

i just want to share with you another

vaccine thats currently in development

also in prostate cancer

and that is

the prospect vaccine also known as psa

tricom

and this is a vaccine that is a poxviral

based vaccine so a little bit different

strategy here coming in with a viral

vector

that targets psa instead of prostatic

acid phosphatase

prostate specific

it also has along with it three

different tcell costimulatory

molecules and remember these are the

things that help the

get the immune system really excited

and within this cassette of genes then

are these are put in

viral poxviral vectors they can be grown

up in large quantities and frozen down

and then when a patient comes into the

clinic you can just simply take this

vial out of the freezer

thought and injected into patients

the idea here is that your immune system

can then be activated to recognize any

psa

containing cells which basically are all

the

the cancer cells

an

initial randomized doubleblinded phase

ii study suggested an improvement in

median overall survival of about eight

and a half months

corresponding to a reduction in the

risk of

death

that was statistically significant

and a phase study

results for this looking at overall

survival are expected later

in 0

the final

group of immunotherapies that id like

to talk about are the adoptive tcell

therapies these can be

the

car t cells

the

tcr transgenic

t cells so these are

t cells that are taken from patients and

modified in a way to help them

identify the tumor with the car t cells

these this

identification

takes place when they take an antibody

fragment and put it on the t cell with

the appropriate signaling domains to

tell the t cell to become activated when

it binds to that target of interest

with a t cell receptor

transgenic basically

theyre taking and modifying the tcells

tcell receptor

and

uh then allowing those cells to grow be

grown up and given back to the patients

in addition

there has been work taken

tumor infiltrating lymphocytes growing

them up and giving them back directly to

the patients without

modifying those t cells

the

of the adoptive cellular therapy

programs the one that is closest to

being approved is the

a car t cell approach

specifically for leukemias

it is anticipated that this will be

approved in the next month or two

so this again looks at

targets that are found on the surface of

bcell lymphomas that

can be easily targeted

make these antibodies and these

antibodies

single fragment

chains can be then

put into vectors and expressed within

the t cell along with the costimulatory

domain

and the signaling domain allowing for

a t cell that is both very effective and

can recognize the

um

the malignant bcell clone very nicely

it will also wipe out normal bcell

clones however

theres typically no significant

bad effects from that

so this is just

an example of one study that was done

with this with a

cd9 car t cell and you can see here

that there was substantial

[Music]

improvement in in survival compared with

what is expected in this disease

where patients that have re

recurrence uh or refractory

um

[Music]

b cell

acute lymphoblastic leukemia

have a very poor prognosis and uniformly

die without treatment

next i want to focus on a few key

immunotherapy concepts

before we finally go to

the

immune side effects that one can see

when were looking at the ability to

get an immune

response within the tumor

microenvironment there are multiple

different layers that one looks at that

could prevent an immune cell from being

active

there are

significant

hostile metabolism mechanisms within the

tumor microenvironment such as acidity

and hypoxia

there are um

the disordered vasculature that can

lead to

decreased ability of the t cells to get

into the tumor micro environment theres

lack of costimulation and antigen

presentation within the tumor micro

environment often mhc molecules will be

down regulated

or

antigens will not be processed correctly

because of the mutations in the tumor

genes there are many

immune suppressive cytokines

and nutrient depleting enzymes like

arginase or ido

and there are the t cell checkpoints

that we talked about

so these can all be

issues that the immune system has to

overcome if theres going to be

effective immunotherapy

youre going to see i believe in the

future more combination studies that

will take this into account and be

adding in

for instance ido inhibitors along with

checkpoint inhibitors and we saw

recent

data at an international meeting on that

the next concept id like to mention is

the concept of antigen spreading and the

tumor immunity cycle

so if you start out with a an immune

response

if you have a dead and dying

tumor cell its taken up by antigen

presenting cells such as the dendritic

cell shown here

the dendritic cell can then present any

of the antigens present within that

tumor to the draining two t cells in the

draining lymph node and can cause

activation of not just

something specific to a vaccine that was

given but maybe a neo antigen that was

present and then this can

lead to a broader army of t cells that

can go back and attack the

the

cancer and this can be an iterative

process that continues to get better

over time and if you

were to flip this on its side and look

at this over time what you would see

perhaps is a tumor that is large

starting out here and maybe if you come

in with a vaccine that

that

that the t cells are specific for lets

say psa in this indication

um

these t cells um all psa positive but

over time maybe theyre

positive for four

different targets within the tumor micro

environment and over time again this

as the tumor is going away maybe theres

a

particular neo antigen that is most

immunogenic in this patient and that

becomes the predominant infiltrate and

this tumor can continue to

to

shrink over time

the next concept id like to talk about

is

the way that the tumor dies may also be

important and so theres this concept of

immunogenic cell death

that is if you come in with a standard

of care agent such as chemotherapy or

radiation perhaps you can kill the tumor

and perhaps the way the tumor dies is

important so

if the tumor undergoes apoptosis or a

or leads to some inflammation those can

be pro protumorogenic however if it

leads to immunogenic cell death that

could actually

incite an immune response that could

help fight the tumor im going to talk a

little bit more about that here

so if you have

for instance

anthracycline cyclophosphamide

oxaloplatin or radiation therapy you

could

lead to killing of a tumor cell in a

manner that leads to upregulation of

these

pathways that will lead to immunogenic

cell death

you can get up regulation of

calreticulin calreticulin

is normally in the endoplasmic reticulum

but it can be translocated to the

surface of the cell as the cell is dying

and this is an important eat me signal

to the dendritic cells the dendritic

cells can come and engulf these dead and

dying

tumor cells and then

identify immunogenic epitopes and

present those to t cells

in addition you can

the dead and dying tumor cell that is

being killed in an immunogenic cell

death pathway can release hmg b which

can

optimally

cause antigen presentation to the

dendritic cells or it can release atp

which could uh act as a find me signal

to the monocytes and

including the dendritic cells and

that could lead to

more mature dendritic cells and

these would then

cause activation of the appropriate t

cells

in a similar vein while you have

immunogenic cell death going on here at

the higher doses of of

either chemotherapy or radiation therapy

at lower doses you can actually cause

a change in the way that the tumor looks

to the immune system making it easier

for the immune system to recognize or

attack the tumor you can get up

regulation of mhc upregulation of

adhesion molecules up regulation of

pools of of peptides

that are are novel

uh and upregulation of fast the death

receptor that that

t cells can bind to

and and kill

or you could get um

some

change in the vasculature making it

easier for the t cells to get in so this

is something we refer to as immunogenic

modulation

in the last section were going to talk

about treating the side effects of of

immunotherapy agents

i think its important

most of what were talking about here is

just talking about the immune checkpoint

inhibitors as those are the things that

are currently on the market vaccines

typically do not lead to

significant adverse events so well be

focusing on

antictla

antipd and antipdl antibodies

so

its important to understand the

unique mechanisms that

these have in normal physiology theyre

involved in maintaining the appropriate

immune response and trying to down

regulate an immune response so if you

block them

you could prevent this this

going back to normal of the immune

system and you could encourage a immune

system thats running amuck

so the type of responses you will see is

an autoimmune type of response and when

you have a patient thats thats coming

in

and

complaining of something i think its

important not to think of the typical

chemotherapy type side effects where if

you have somebody coming in with

diarrhea oh i will treat with imodium

no you dont want to do that in this

case necessarily you want to think

potentially

this patient has an underlying

autoimmune type of response

lets treat the underlying condition

and not just

symptomatically treat

more like a graft versus host type of an

effect

this was a recent

article

that

i think is very interesting showing

the relative risk of adverse events in

patients treated with immune checkpoint

inhibition

versus chemotherapy across a variety of

different studies and what you can see

here is that for any grade

adverse events there was a trend towards

improved outcomes

decreased side effects if you had

the

immune

checkpoint inhibitor but if you looked

at just the high grade adverse events it

was substantially better if you had the

checkpoint inhibitor than if you had

chemotherapy

another way of looking at that same data

set is that for any

uh all grade

adverse events you had about an

reduction in the risk of adverse event

if you had the immune checkpoint

inhibitor

but for high grades you had about a

reduction in the risk of a highgrade

adverse event and treatment

discontinuation about a

improvement in

[Music]

likelihood of

disease treatment discontinuation

and treatment related deaths also

a

decrease risk

when you think of the immune related

adverse events they can affect virtually

any organ in the body or any organ

system

and you can get

these at any time its not a

always an exact time after treatment as

youd expect for chemotherapy where

youd expect your neutropenia to be

seven to 0 days after the chemotherapy

this can be literally any time

afterwards

this is an initial

paper that was done in 0 looking at

the kinetics of immune related adverse

events

but you can see that while rash may be a

little bit earlier you can have a wide

variation

over a number of weeks

after initiation of

of treatment and it can be

within one week after initiation of

treatment

liver toxicity typically later

hypophysitis and diarrhea also can be

virtually any time

typically when we treat these immune

related adverse events are drug of

choice

or drug category of choice is the

glucocorticoids

and whether its prednisone

dexamethasone methylprednisolone

hydrocortisone cortisone all of them

work well

typically

occasionally well need to

go down and

add in additional therapies on top of

the glucocorticoids

when theres a particularly severe or

refractory case

lets talk a little bit about

dermatologic toxicity

often this presents

three or more weeks after initiating

immune checkpoint inhibition

typically its mild you can get a

macular papular rash there may be some

itching burning tightness

if it involves

up to 0 percent of the bodys total

body surface area then its considered

to be mild and you can use

topical steroids

and

symptomatic management

if it involves up to 0 0 to 0 this is

considered to be more moderate and

topical steroids can be used but you

could start systemic

steroids if theres no improvement

within a week

the more severe

skin manifestations include blisters

dermal ulceration

necrotic bullish or hemorrhagic

lesions

in this case you would definitely want

to start

parental

corticosteroids

or if if the patient can tolerate it

oral steroids

vitiligo and does not require treatment

so im going to show you some pictures

of some more severe cases

this is

this is patients with stevensjohnson

syndrome you can see here these oral

lesions

here

you can see

toxic epidermal necrolysis

and and these lesions on the back of

this patient here

this is

rare but if it happens you need to

institute

steroids immediately

vitiligo on the other hand does not

require treatment and apart from

cosmetic changes really doesnt bother

the patient

so lets talk about a patient example

here

this is a patient who

is on

nivolumab for his nonsmall cell lung

cancer

and he comes into the emergency

department complaining of some diarrhea

so

again heres a patient where you dont

want to

assume

that theres been some food poisoning or

just ate something bad you want to

assume that there may be colitis going

on here so you do want to get some stool

studies to work this up but you want to

be thinking all along this maybe colitis

we may need to treat

so

when do you treat somebody with colitis

well if its grade one if theres less

than four stools a day

then you may not need to

do anything different

but you will need to tell them if that

it increases in number of stools per day

you you will need to treat if its grade

you definitely want to hold the

therapy you may want to stop

discontinuing the therapy altogether but

you may be able to reinstitute if you

can get them through the diarrhea

relatively quickly

oftentimes just discontinuing the

therapy will be good enough however if

they

continue to have diarrhea for a

prolonged period of time more than seven

days

then you would want to institute

glucocorticoid treatment if there is

greater than seven stools greater or

equal to seven stools a day over

baseline

then

you want to initiate a glucocorticoid

treatment we typically make our patients

npo here

and we typically give

parenteral steroids

hepatotoxicity is something that is

commonly seen with

all of the immune checkpoint inhibitors

often it can happen

eight to weeks after initiation of

therapy

its important to remember

to review the patients medications to

avoid anything that could be

exacerbating underlying hepatotoxicity

and to tell the patients to avoid

alcohol ingestion

grade two toxicity if you have a ast or

alt between two and a half and five

times upper limit of normal or bilirubin

between one and a half and three times

upper limit of normal typically you can

give

a intermediate to highdose

glucocorticoids

and then a slow taper over about a month

if you have grade three or greater

toxicity you want to admit those

patients you want to start

iv methylprednisolone and and if patient

doesnt

improve you may want to

increase your

immune suppression

endocrinopathies are a common side

effect with these immune checkpoint

inhibitors

anything from the thyroid the adrenal

glands

can be affected

if its just asymptomatic tsh

change then theres

really no need to discontinue anything

you can just continue the immune

checkpoint inhibitor and monitor the tsh

and

if you need to

give um synthroid you can certainly do

that if theres symptomatic

endocrinopathy you

will

often need to delay the

the immune checkpoint inhibitor

and

initiate appropriate treatment

if you have

a suspicion of adrenal crisis then

youre going to need to give highdose

stress those steroids

and

appropriate

fluid resuscitation

hypothesitis is one of these

endocrinopathies that

is important to understand because it is

not something that the typical medical

oncologist is used to dealing with

often patients will complain of fatigue

headaches visual field defects

workup includes getting a variety of

of hormones that are affected by

the

pituitary acth tsh fsh lh growth hormone

and prolactin

imaging will often

reveal an enlarged pituitary gland

typically the pituitary gland shrinks

over time and this may be uh

in an 0

year old patient it may be

just back to a normal size for a

0 year old patient

after two one to two months um

after initiating therapy is when you

normally or you when you often see the

first

evidence of hypophysitis

and when this happens glucocorticoids

are recommended

typically starting with high dose and

then

can can taper but

based on on symptoms in part

other endocrinopathies include the

hypothyroidism

its appropriate there to give the

levothyroxine replacement as we

discussed

hyper

we should also

be aware that you can get

hyperthyroidism

and

this is typically due to acute

thyroiditis because of the immune

activation typically this will

resolve and then lead into

hypothyroidism

it can also be adrenal insufficiency as

as we already mentioned

pneumonitis is something that occurs

with

antictla

as well as antiped and antipdl

inhibitors

often this is occurs later and

can

be seen with a new cough or dysmia as

the presenting symptoms in most of the

cases

if this leads to

moderate symptoms

you which is a grade two you would want

to admit the patient and begin

steroid treatment

if it is

severe symptoms or lifethreatening

symptoms it requires oxygen

youd also want to admit the patient

start the

steroids and you want to have a long

taper of those steroids and

with a low threshold to

reinitiate

escalation of the steroids if

symptomatic improvement

stalls

there can also be pancreatic immune

related adverse events elevation of

amylase and lipase often are

asymptomatic

and if there is no

symptoms

often you can just monitor those

patients however if there is symptoms

you hold therapy and and

treat with steroids if indicated

in addition to the exocrine pancreas the

uh endocrine pancreas can be affected

although this is less common but if

somebody uh presents with new

diabetic ketoacidosis

you want to

treat them as a diabetic and

have aggressive treatment of that

diabetic ketoacidosis

there are many other

organs that can be affected

the heart

red blood cells

um

and in a variety of different

organs

you should always keep an eye out

for these typically they are managed

with steroid treatment

and symptomatic

management the next case i just want to

go through and this is the final case

that well go through is a year old

male that also had nonsmall cell lung

cancer

patient was started on immunotherapy

eight weeks ago for lung cancer now he

comes in complaining that his vision is

blurry his glasses dont work anymore he

denies any eye pain but he does say that

he has a mild headache because he reads

a lot at work and his glasses arent

working anymore

on examination

you

look at his visual acuity and

without his glasses on hes okay in his

right eye 0 over but in his left eye

his vision is

substantially diminished

you look in his pupillary

reflect

is

fine

but when you look at his visual fields

he has a temporal loss

in his right eye and

and so you say okay what could be going

on here

you

do the appropriate work up which would

include either a ct or mri of the head

to look at the pituitary

and you get the pituitary labs here

and what you find is that his pituitary

is quite enlarged as you can see here on

this imaging

and

you diagnose him then with hypophysitis

and so treatment again for him would be

glucocorticoids

and then

after improving the symptoms you would

switch to oral

glucocorticoids

so kind of wrapping it up here the

immune related adverse events management

there are

important considerations when were

thinking about the

mechanism of these immune checkpoint

inhibitors and

its important to

understand what those mechanisms are

when you are trying to figure out the

best way to treat them

so always have a high suspicion of

immune related adverse events in

patients on immune checkpoint inhibition

who can often present just with vague

symptoms like im not feeling right and

then you find out that theyre

you know

theyre

they have hypophysitis

or they may have a mild headache

you want to emphasize to patients to

contact you

if

there are

any

symptoms at all

because we want to catch this early to

to treat what could

be a very serious

event

and especially in cases like colitis

dont just blame it on the burger you

had last night

most immune related adverse events occur

within the first few months of starting

therapy because it

is

based on an underlying

immune response that can be uncovered by

the uh

by the immune checkpoint inhibition and

if it isnt uncovered in the first

couple of months it probably isnt there

to begin with

but it can present late in

[Music]

the

course and it could be even after

discontinuing the drug so always be

vigilant for that

finally if you combine

immune checkpoint inhibitors pdl and

ctla or pd and ctla inhibitors

together

this substantially increases the

risk of an immune related adverse event

in general

when you have

moderate

when you have mild toxicities you may

not need to hold the treatment but when

you have moderate or worse toxicities

you should at least hold the treatment

and often need to

start the

glucocorticoid treatment

when initiating immunosuppressive agents

there are special risk groups including

those that are ppd positive

or

hep

c or

or b

positive if they have latent

antigens you could cause reactivation of

those if you give prolonged

glucocorticoids

you should also for prolonged

glucocorticoids put patients on pcp

prophylaxis

steroids should be given at high dose

early

and

the taper should be slow

often treatment of the immune related

adverse events requires a

multidisciplinary team

because of the different organ systems

that they may

be targeting

so in conclusion what ive tried to

share with you is that immunotherapy can

lead to rapid

deep and most importantly durable immune

responses and have changed the way that

we

see and evaluate patients with cancer

in our clinics

immunotherapy may in some cases be

curative

and in other cases may lead to longterm

disease control

future efforts in combination therapy

are seeking to expand the proportion of

patients with clear clinical benefit

and these combination therapies should

not focus not only on generating an

antitumor immune response but making

sure that those effector cells

are functional within the tumor micro

environment

immune related adverse events are

typically transient and manageable but

should be identified and treated

promptly and overall

immunotherapy which leads to these deep

durable responses is better tolerated

than chemotherapy

thank you so much for your attention

you