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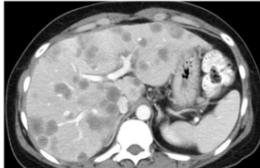
Dr. Guru Sonpavde is the Bladder Cancer Director at the Dana-Farber Cancer Institute in Boston, Massachusetts. He completed his Medical Oncology Fellowship at Indiana University. His primary focus is the development of new drugs and combinations to treat urologic cancers with a focus on bladder cancer. He has also refined prognostic classification and clinical endpoints across multiple urologic cancers. He is the co-chair of the Genitourinary Oncology Committee of the Hoosier Cancer Research Network and a member of the GU Committee of Southwest Oncology Group.

Dr. Sonpavde: I'm a Medical Oncologist, I treat more advanced stages of the cancer. On this slide here I'm showing you the treatment of metastatic bladder cancer. The picture on the right there shows you a patient with a metastasis or spread of cancer to the liver. You see all those dark spots on the liver. So it can be an aggressive disease when it spreads outside the bladder, through the bloodstream, into distant organs like the liver, lung, bones, and other organs.

Medical Oncology

Metastatic bladder cancer treatment options

1. Physically active and Fit patients with good kidney function:
 - Combination of intravenous chemotherapy drugs containing cisplatin (survival ~15 months, ~10-15% survive 5 years)
2. Physically less active Unfit patients or those with other serious illnesses or poor kidney function:
 - Combination of intravenous chemotherapy drugs containing carboplatin (survival ~9 months, none survive 5 years)
 - Immunotherapy: Pembrolizumab or Atezolizumab intravenously (long-lasting responses in ~25% of patients)
3. Trials:
 - Combination of 1) chemotherapy + immunotherapy and 2) immunotherapy + immunotherapy



So how do we treat these patients? So on the left-hand side you see the bullet point number one. So in patients who are fit and active with good kidney function, we give them a combination of chemotherapy drugs intravenously, like a drop. And one of these drugs includes the drug called cisplatin. In patients who are less

active, less fit, because of either other illnesses or high volume of cancer or if they have poor kidney function, they're not fit for cisplatin. And so in these patients, we give them a different combination of

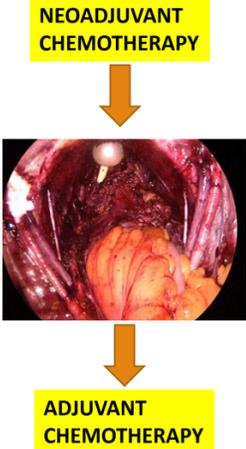
chemotherapy drugs including carboplatin, which is a gentler version of cisplatin. And again, this is an intravenous drip. The other option we have now in the past year, couple years, is giving immunotherapy drugs instead of chemotherapy in patients who are not fit for cisplatin. So that includes drugs like pembrolizumab or atezolizumab, which are both approved to give intravenously to boost the immune system. And that has also been shown to be active and induce this long-lasting responses in a quarter of patients. And the third option you see down there is trials or research. We don't cure most patients with this disease once it spreads out, so we always want to offer trials and research with new drugs or combination of chemotherapy and immunotherapy drugs or combinations of promising immunotherapy drugs.

In this slide here I show you the treatment of muscle-invasive bladder cancer. This is a little bit earlier stage, it's not metastatic. It's confined to the bladder, but it's invading the muscle layer so it's deeper than the lining. And so this is a state in which although it is confined to the bladder, there is a high risk of it spreading out and hiding in other places in the body.

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Muscle-invasive bladder cancer treatment options

1. Pre-operative (neoadjuvant) chemotherapy:
 - Combination of chemotherapy drugs containing cisplatin given intravenously before bladder removal surgery (radical cystectomy)
2. Post-operative (Adjuvant) chemotherapy:
 - Combination of chemotherapy drugs containing cisplatin given after radical cystectomy
3. Immunotherapy:
 - Research is testing the value of immunotherapy before or after radical cystectomy



The diagram illustrates the timing of chemotherapy in the treatment of muscle-invasive bladder cancer. It features a central photograph of a bladder during surgery. Above the photograph, a yellow box labeled 'NEOADJUVANT CHEMOTHERAPY' has a downward-pointing arrow leading to the top of the bladder. Below the photograph, another yellow box labeled 'ADJUVANT CHEMOTHERAPY' has an upward-pointing arrow leading to the bottom of the bladder. This visualizes that neoadjuvant chemotherapy is administered before the bladder is removed, while adjuvant chemotherapy is administered after the removal.

Therefore, we really want to give this patient chemotherapy intravenously or other types of therapy intravenously to kill cancer cells that might be hiding far away. That is in addition to taking the bladder out. So the first bullet point there shows pre-operative chemotherapy, that's chemotherapy given before radical cystectomy. It's also called neoadjuvant chemotherapy, which has been shown to improve the survival of patients with bladder cancer invading the muscle if given before the bladder is removed. And then the second option is post-operative, or adjuvant, chemotherapy. This is chemotherapy given after the bladder comes out and this also has been shown to improve survival in other smaller studies. And so this is a second option in these patients, although we prefer giving chemotherapy before taking the bladder out. And the third option is immunotherapy, this is still a research option. There are research studies going on looking at whether immunotherapy alone, without chemotherapy, given after the bladder is removed can improve the survival of these patients.

So there's a picture on the slide right shows you the way we give neoadjuvant chemotherapy, that's before the bladder comes out, and adjuvant chemotherapy is done after the bladder comes out.

And this third slide here, in the Medical Oncology section, shows you what we're giving patients when the cancer grows after chemotherapy. So this is called salvage chemotherapy or second-line therapy. So all the chemotherapy drugs have been not very effective but now we have five exciting options of immunotherapy that are approved in patients where the cancer is growing and metastatic after

chemotherapy. These are the five drugs listed there: the pembrolizumab, atezolizumab, durvalumab, nivolumab, avelumab. Now all of these drugs don't cure patients, they generally improve outcomes, they help people live longer, and some patients who respond might have a long duration of response. But we

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Second-line therapy for metastatic cancer growing after previous chemotherapy: 5 immunotherapy drugs approved in US:

1. Pembrolizumab
2. Atezolizumab
3. Durvalumab
4. Nivolumab
5. Avelumab

Research trials of new drugs should be strongly considered

Overall Survival: Total

	Events, n	HR (95% CI) ^a	P ^b
Pembro	170	0.70	0.0004
Chemo	196	(0.57-0.86)	

Median (95% CI):
10.3 mo (8.0-12.3)
7.4 mo (6.1-8.1)

^aBased on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (110 vs 115 g/L), and time from completion of chemotherapy (<1 vs ≥1 mo). ^bTwo-sided P-value based on stratified log-rank test. Data cutoff date: January 16, 2017.

generally cannot cure patients with these drugs; therefore research trials testing new drugs is a big consideration in patients where the cancer is growing after previous chemotherapy.

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