Dana-Farber Cancer Institute | BWH BRIGHAM AND WOMEN'S HOSPITAL

DANA-FARBER/BRIGHAM AND WOMEN'S CANCER CENTER

Genitourinary Cancer Management During COVID-19 Pandemic – Dana-Farber/Brigham and Women's Cancer Center Proposed Clinical Guidelines

Genitourinary Cancer Treatment Center
Dana-Farber/Brigham and Women's Cancer Center
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As the COVID-19 pandemic puts stress on the health system overall, oncologists are forced to adjust their practice to optimize care for patients with cancer. A recent WHO-China Joint Mission report indicates that patients with cancer and COVID-19 were twice as likely to die as patients with no comorbid condition (7.6% vs. 3.8%). Meanwhile, cancer type-specific data is sparse due to low number of patients; a few reports have suggested poorer outcomes in patients with heterogeneous tumors of varying stages, but these data are entirely from outside the US and may not be generalizable.

The following is intended to provide guidance to healthcare providers at Dana-Farber/Brigham and Women's Cancer Center, as well as its satellites and referring doctors. These GU-specific guidelines were suggested, discussed, and revised by our group, and they are subject to change as more information becomes available, or as government/hospital policy evolves. Please note that professional societies such as ASCO and ESMO, as well as journals focusing on specific subtypes and disease areas are starting to build their own consensus-based guidelines. If you have questions, please contact the Lank Center for Genitourinary Oncology at (617) 632-2682 or dfcigucreferrals@dfci.harvard.edu.

General considerations during COVID-19 pandemic

1. Avoid, if possible, using immunosuppressive steroids - be more risk-averse considering therapies with chance for adverse events that require immunosuppressive intervention with steroids
2. Minimize hospital exposure - when possible and sensible, defer clinic visits and/or pursue therapies with fewer infusion cycles, and increase use of telemedicine
3. Patients receiving systemic cytotoxic chemotherapy at risk for neutropenia (e.g. docetaxel, cabazitaxel, BEP chemotherapy) should receive G-CSF support and ideally "self-quarantine" except for medical visits

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Bladder Cancer

1. Low grade (Ta, noninvasive)

- Continue with surveillance regimens and consider spacing out typical intervals between cystoscopy

2. Intermediate risk disease

- Consider extending intervals between surveillance cystoscopy or maintenance regimens on a case by case basis

3. High risk disease (T1)

- Begin with induction BCG and consider first cystoscopy in 3 months. For maintenance and surveillance cystoscopy, try to adhere to guideline therapy recognizing that intervals may extend to 3-4 months initially

4. Muscle-invasive bladder cancer (MIBC, T2-T4aN0)

- Consider standard neoadjuvant chemotherapeutic agents followed by radical cystectomy within 8 weeks after the last chemotherapy and upfront radical cystectomy or trials of neoadjuvant immunotherapy and targeted therapy for cisplatin-ineligible patients
- Radiation therapy - We consider instituting a hypofractionated regimen for MIBC, which is supported by a randomized trial and decreases daily treatment (5 days a week) duration from 7 weeks to 4 weeks. Palliative hypofractionated or even single fraction of stereotactic body radiotherapy (SBRT) may be considered for symptomatic metastatic disease

5. Systemic therapy for metastatic disease

- MIBC - Chemotherapy will be modified whenever possible to decrease the extent of myelosuppression, yet aim to maintain intensity in this curative setting:
  - a. Avoid myelosuppression:
    - Choice of chemotherapy (e.g. gemcitabine + cisplatin rather than MVAC or dose dense MVAC)
    - Use growth factor support liberally for age and comorbidities
    - Use 3 cycles instead of 4 cycles in lower risk cT2N0 patients
  - b. Adjuvant chemotherapy may be initiated up to 3 months after radical cystectomy since no clear data show that extremely early adjuvant chemotherapy improves outcomes; Neoadjuvant chemotherapy should be initiated promptly in cisplatin-eligible patients.
  - c. In patients receiving neoadjuvant chemotherapy, imaging may be repeated at the end of all chemotherapy without necessity of mid-course imaging unless there are symptoms suggesting progression of disease

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d. Choose upfront radical cystectomy for predominant variant histology MIBC, which is the current convention

e. Surveillance following completion of therapy may be conducted by telemedicine visits with imaging guided by symptoms or laboratory assessments

- Advanced disease - More generally, in the metastatic palliative setting, efforts will be made to decrease the extent of myelosuppression from chemotherapy:

a. Regimen intensity may be decreased in incurable patients with visceral metastasis and/or ECOG PS 2 (e.g. dose reductions, 4-week cycles instead of 3-week cycles)

b. Use growth factor support liberally for age and comorbidities

c. Some regimens may be delayed with weekly monitoring using telemedicine, especially in patients with low volume, minimally symptomatic and indolent disease

d. In patients who are likely to derive very little benefit and are at risk of toxicities due to comorbidities or poor ECOG-PS, hospice should be strongly considered

e. In patients with FGFR3/2 genomic alterations, would favor the non-myelosuppressive drug erdafitinib over the moderately myelosuppressive enfortumab vedotin

f. Consider first-line pembrolizumab instead of chemotherapy in cisplatin-ineligible patients with high tumor PD-L1 expression

g. We will increase the interval between in-person whenever possible and use telemedicine resources extensively (e.g. enfortumab vedotin may be given weekly for 2 weeks followed by a week off rather than 3 weeks on followed by 1 week off)

h. The interval between objective imaging assessment will, whenever feasible, be increased if the patient is clinically stable or improving and tolerating therapy

i. Follow-up after completion of therapy in responding patients may be conducted by telemedicine visits complemented by laboratory assessment when necessary, with imaging as dictated by symptoms or burden of disease

6. Trials may require more visits and lab assessments/imaging, but may be considered carefully in selected cases where substantial benefit over current standard of care is anticipated

Kidney Cancer

1. Localized mass

- While the general recommendation is for our patients to receive the standard of care treatment that suits their personal preferences and life expectancy, our ability to treat kidney masses concerning for kidney cancer is currently limited by the COVID-19 pandemic, especially surgery

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- For patients with disease that is confined to the kidney (stage T1 and T2) who opt for surgery, we recommend deferring surgery until normal services are resumed. Based on available data, it is unlikely that this would cause significant harm. Alternatively, there may be an option to pursue thermal ablation or radiation for therapy
- For patients with disease that is locally advanced (stage T3), we believe that treatment should be initiated sooner than later. As an alternative to immediate surgery, there may be an option for neoadjuvant therapy to control or shrink the burden of disease followed by surgery at a later date

2. Adjuvant therapy

- While sunitinib is approved based on STRAC data showing an improvement in DFS, to date, 4 other trials were completely negative, and no trial has shown an improvement in OS with therapy in the adjuvant setting
- Adjuvant trials, if available, should be well understood with clear expectations before consenting, with the knowledge patients can be randomized to no-therapy/placebo
- Immunotherapy is intriguing with trials ongoing but should not be offered outside of a clinical trial; in current situation where potential benefits are unknown, monitoring patients following nephrectomy per NCCN guidelines without any therapy is reasonable

3. Metastatic disease

- For patients with metastatic disease (stage T4), surgery should not be considered. The use of systemic therapy is equivalent to upfront surgery in most cases, and thus surgery is reserved for select situations where symptoms are intractable or systemic therapy is unavailable
- While numerous retrospective analyses have shown a benefit to the role of cytoreductive nephrectomy in the initial management of advanced renal cell carcinoma, the CARMENA trial did not show a benefit to upfront CN versus proceeding directly to systemic therapy. While there is discussion regarding outcomes of the trial given increase in poor risk disease, this trial emphasizes importance of upfront systemic therapy. Especially during pandemic where surgery options are limited, we would defer cytoreductive nephrectomy unless severe symptoms from the primary mass (pain, hematuria, etc). While it is standard to pursue cytoreductive nephrectomy with localized therapy to metastases for oligometastatic disease, could defer surgery with trial of systemic therapy (see below) until surgery timing is feasible

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- IMDC risk classification remains an important tool in determining the appropriate therapy. IMDC risk classification is based on readily available clinical data (time from diagnosis to initiation of therapy <1 Year, KPS <80, Hemoglobin < LLN, Platelet > ULN, Neutrophil > ULN). When deciding systemic therapy, goal is to limit visits to hospital while also decreasing risk for possible pulmonary toxicities or immunosuppression with high dose steroids

  a. Favorable risk disease (No risk factors) - For those with favorable risk disease, surveillance or deferred therapy should be strongly considered. This is supported by phase II data from Rini et al. wherein 48 patients' median time on surveillance from registration until initiation of systemic therapy was nearly 15 months; multivariate analysis showed that higher numbers of IMDC adverse risk factors ($p = 0.0403$) and higher numbers of metastatic disease sites ($p = 0.0414$) were associated with a shorter surveillance period. If treatment is to be pursued after discussion with patient, single agent VEGF therapy could be considered given favorable toxicity profile with no risk for irAEs that could require high dose steroids. Checkmate 214 shows trend toward improved ORR and PFS with sunitinib monotherapy, and while the combination of pembrolizumab and axitinib showed improvement in OS independent of IMDC risk classification, on 18 month followup improvement in OS was less robust with HR approaching 1 for those with favorable risk disease. While cabozantinib was studied front line in only intermediate or poor risk disease, its approval in front line setting is not limited to those with intermediate or poor risk disease and this could be considered

  b. Intermediate/Poor risk disease – Despite the risk for irAEs with subsequent need for high dose steroids, a combination regimen containing immunotherapy is the standard, with combinations of nivolumab/ipilimumab and pembrolizumab/axitinib showing improvement in OS when used in the front line setting. While each is effective, they are associated with different toxicity profiles and response rates. While nivo/ipi has longest followup with highest CR rate, 40% of patients needed high dose steroids, and pembrolizumab/axitinib is also associated with irAE (though number of patients requiring high dose steroids has not been reported). Axitinib/avelumab is appealing given <12% required high dose steroids but this benefit is outweighed by need for infusions every 2 weeks as opposed to every 3 weeks for the other regimens. The following factors play into the decision regarding front line therapy

  c. Sarcomatoid differentiation – While any ICB containing regimen is active in those with sarcomatoid differentiation the differential response for nivo/ipi (40-60%) with CR rate of 20% makes nivo/ipi appealing in this situation

  d. Visceral crisis – if patient with pending visceral crisis requiring response, would pursue combination of pembrolizumab/axitinib given ORR approaching 60%

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4. Dosing of Therapy

- Immunotherapy can be delayed or postponed as needed in maintenance setting given prolonged half life of the antibody and particularly if already received over 6 months of therapy and had a PR/CR. During initial dosing of nivo/ipi, can extend dosing after 3 months if any concern for potential irAE to minimize need for high dose steroids

5. Variant histology

- Single agent VEGF remains gold standard in non-clear cell setting despite phase 2 trials showing activity of pembrolizumab or atezolizumab/bevacizumab. Retrospective data on cabozanitnib in this setting supports its use as another treatment option

6. Second line therapy

- Given lack of randomized data, we would not rechallenge with immunotherapy following immunotherapy in the front line setting to minimize risk for irAE and high dose steroids. Cabozantinib, lenvatinib/everolimus, axitinib are all reasonable options if patient has not seen in the front-line setting

Prostate Cancer

1. Localized prostate cancer

- Treatment can be safely deferred in all patients with low risk prostate cancer. DRE and repeat biopsies can be safely deferred by >3 months in most patients on surveillance, with earlier evaluation recommended only in patients with rapidly rising PSA or symptomatic progression
- Treatment can be safely deferred in most patients with favorable intermediate prostate cancer. For patients with favorable intermediate risk planned for primary radiohormonal therapy, ADT start can be safely deferred in most patients, but earlier ADT start could be considered in clinical situations concerning for more aggressive disease biology (rapidly rising PSA, abutting the capsule of the prostate or seminal vesicles on MRI, etc.)
- For patients with unfavorable intermediate risk prostate cancer or high/very high risk prostate cancer planned for primary radiohormonal therapy, initiation of androgen deprivation therapy with LHRH agonist or antagonist should not be deferred due to COVID-19. Radiation can be safely delayed until months 5 and 6 of ADT for intermediate risk or high risk disease without concern for poorer outcomes
- For patients with intermediate risk prostate cancer planned for surgery, neoadjuvant ADT is not recommended

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- Patients with high/very high risk prostate cancer planned for surgery can be assessed for candidacy for neoadjuvant/adjuvant ADT+/- apalutamide per 19-140 PROTEUS. For patients who are not interested in or not a candidate for PROTEUS, neoadjuvant ADT could be considered to prevent progression while awaiting surgery – risks/benefits of this approach should be discussed with the patient and would need to be approved by insurance

2. Biochemically recurrent prostate cancer

- For patients who have had prior prostatectomy with rising PSA to >0.1 and are candidates for salvage radiohormonal therapy, initiation of androgen deprivation therapy with LHRH agonist or antagonist should not be deferred due to COVID-19. Radiation can be safely delayed until months 5 and 6 of ADT without concern for poorer outcomes
- For patients with rising PSA not planned for salvage radiohormonal therapy, initiation of ADT can usually be safely deferred, with consideration of initiating ADT only with elevated and apidly rising PSA
- For patients with non-metastatic CRPC who planned for salvage local therapy with curative intent, initiation of systemic therapy for nmCRPC (enzalutamide, apalutamide, darolutamide) should not be deferred due to COVID-19. For patients with nmCRPC being treated with palliative intent, initiation of systemic therapy for nmCRPC (enzalutamide, apalutamide, darolutamide) can be safely deferred for patients with PSA-DT >10 months; for patients with PSA-DT <10 months these agents can be initiated per clinician judgment of risk/benefit

3. Metastatic prostate cancer

- LHRH-agonist/antagonists
  - a. For macrometastatic prostate cancer, initiation of ADT with LHRH agonist or antagonist should not be deferred due to COVID-19
  - b. LHRH agonists are favored over LHRH antagonists for maintenance (except when clinically indicated) due to availability of longer depot doses; orchiectomy should be delayed until after resolution of COVID-19 situation
  - c. LHRH-agonists can be reasonably be delayed per clinician judgement of likelihood of testosterone recovery during period of dose delay based on patient factors (age, prior duration of LHRH-A treatment, etc.)
  - d. Longer depot forms of LHRH agonist (i.e. leuprolide 30 mg 4-month depot, leuprolide 45 mg 6-month depot) are favored when feasible
  - e. LHRH-A can be deferred indefinitely for patients on abiraterone
  - f. LHRH-A can be safely deferred in patients on potent AR antagonist (enzalutamide, apalutamide or darolutamide) for longer than patients on ADT alone

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- Metastatic hormone-sensitive prostate cancer
  a. Docetaxel can be safely deferred for up to 120 days after starting on ADT; AR pathway inhibitor can be safely deferred for up to 90 days after starting on ADT. Decision to delay further is dependent on risk/benefit with relation to both cancer and COVID-19-related issues i.e. patients responding well to ADT alone who are at risk for severe complications from COVID-19 infection may reasonably delay treatment intensification even further
  b. Even in chemo-fit patients, AR pathway inhibitor may be preferred over docetaxel in patients with risk of severe complications from COVID-19 infection (advanced age, unstable or communal living situation, notable cardiovascular or pulmonary comorbidities)
  c. Potent AR antagonist may be particularly preferred over abiraterone in patients who would have difficulty with intensive laboratory and BP monitoring during the COVID-19 situation, and in patients with known cardiovascular issues
  d. Potent AR inhibitors are to be used with caution in patients at risk for falls/fractures, if abiraterone is also not preferred, these agents can be prescribed at a dose reduction through the duration of the COVID-19 situation with consideration of dose escalation upon resolution
- Metastatic castration-resistant prostate cancer
  a. Choice between chemotherapy and AR pathway inhibitor follows similar principles as for hormone sensitive disease, except risk/benefit may favor chemotherapy over 2nd hormonal agent in patients with symptomatic/rapidly progressing disease
  b. Sipuleucel-T can be safely delayed in most patients appropriate for this modality given its indication for asymptomatic/minimally symptomatic disease usually early in the transition to castration resistance
  c. Radium-223 can be administered and is unlikely to be immunosuppressive, but doses can be safely delayed as needed for concerns regarding COVID-19 exposures

Testicular Cancer

1. Therapy for curative intent should not be delayed.
2. For clinical stage 1 seminoma or non-seminoma after orchiectomy, surveillance is preferred over adjuvant therapy (chemotherapy, radiation therapy or RPLND) regardless of risk group
3. For stage 2 or 3 seminoma or non-seminoma, bleomycin should be excluded to the degree possible with preference for:
   - 4 cycles of EP (rather than 3 cycles of BEP) with for good risk disease
   - 4 cycles of VIP (rather than 4 cycles of BEP) for intermediate/poor risk disease