

How can we better harmonize eligibility criteria for clinical trials of adjuvant therapies in bladder cancer?

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Disease and patient characteristics

- Histology
 - Inclusion/exclusion of variant histologies
 - Small cell and other variants
 - Central pathology (practicality/expense)
- Perioperative chemotherapy
 - How much NAC is sufficient?
 - Definition of cisplatin ineligibility
 - Patients “refusing” adjuvant chemotherapy as a distinct patient population

Histology

- Current state of eligibility on CPI adjuvant studies
 - CA209274 - Dominant component of histology needs to be urothelial carcinoma or transitional cell carcinoma. Foci of varied histologies (eg, minor variants) are accepted
 - IMvigor010 - Patients with mixed histologies are required to have a dominant transitional cell pattern
 - A031501 - Variant histology allowed as long as urothelial carcinoma is predominant (>50%). Pure small cell carcinoma is excluded

Histology continued

- Wide spectrum of divergent histologic differentiation – squamous, glandular, micropapillary, sarcomatoid, small cell, clear cell, lymphoepithelial, plasmacytoid, etc.
- 10-80% UCs in bladder with variant histologic differentiation
- 40% high-grade UC renal pelvis with variant histologic differentiation (Mod Pathol. 2006 Apr;19(4):494-503)
- 25% TURBTs with UC show variant histologic differentiation (Urology. 2007 Jul;70(1):69-74)
 - 100% high grade and 99% invasive
 - Most common – squamous (40%) and glandular (18%)
 - UCs with mixed histologic features were associated with muscle invasion at TURBT (chi-square test, $P < 0.001$) and with extravesical disease at cystectomy (chi-square test, $P = 0.0001$). The presence of mixed histologic features at TURBT was an independent predictor of extravesical disease in a multivariate logistic model ($P = 0.007$)

Histology continued

- Potential prognostic implications
 - Associated with locally aggressive disease (Urology. 2007 Jul;70(1):69-74)
 - Predicts LN involvement (Hum Pathol. 2007 May;38(5):741-6)
 - Worse prognosis (Urology 2005 Nov;66(5):1122-6)
- Potential therapeutic Implications
 - Presence of squamous or glandular differentiation does not confer resistance to MVAC – secondary analysis of S8710 (BJU Int. 2011 Sep;108(5)693-9)
 - Micropapillary variant (Cancer 2007; 110:62-7 and BJU Int. 2013 Jun;111(8):E325-30)
 - NAC benefit yes/no
 - Lymphoepithelioma-like (BMC Urol. 2017 Apr 27;17(1):34)
 - Chemo-sensitivity
 - Small cell (J Clin Oncol. 2009 Jun 1;27(16):2592-7)
 - Alternative small cell-directed chemotherapy regimen e.g. EP



Histology continued - central pathology

- Variant (divergent) histologic differentiation under-recognized in community practice. Impact of mandatory central pathology review at a large referral hospital (Urol Oncol. 2013 Nov;31(8):1650-5)
 - 589 TURBTs, 115 (19.5%) UCs with variant histologic differentiation
 - Variant histologic differentiation not documented by referring institution in 44% cases (47% were extensive i.e. > 50%)
 - Squamous differentiation (32%) was the most common variant histology identified, followed by small cell (16%), glandular (13%), micropapillary (12%), nested (8%), sarcomatoid (6%), lymphoepithelial (3%), and plasmacytoid (1%) type
 - Commonly under-recognized patterns included lymphoepithelial (2) and plasmacytoid (1) types (100%), nested (7, 87%), micropapillary (10, 83%), and small cell (7, 44%)
 - Emphasizes the importance of central pathology review in the management of bladder cancer patients and the need for increased awareness of this relatively common phenomenon in UC



Histology summary

- Should variant histology be allowed and if yes, how to define?
 - Variant histology is a common finding in UC
 - Limited data suggests worse outcome with certain variants
 - Small cell – distinct biology and typically managed like small cell arising in other organs e.g. lung
 - Sarcomatoid
 - Micropapillary
 - Limited data suggests therapeutic implications
 - Small cell
 - Micropapillary
 - Lymphoepithelial
- Should central pathology review be required?
 - Under-recognition of variant histology is not uncommon
 - Issues of practicality and expense



Neoadjuvant chemotherapy – How much is sufficient?

- Current state of eligibility on CPI adjuvant studies
 - CA20927 does not define NAC chemotherapy
 - IMvigor010 defines NAC as at least 2 cycles of a platinum-containing regimen
 - A031501 does not define NAC

Neoadjuvant chemotherapy continued

- Phase 3 NAC trials

- S8710 (Grossman et al. NEJM 2003). 3 cycles MVAC – 87% received at least one full cycle of MVAC
- BA06 30894 Trial (JCO 2011 29;16). 3 cycles of CMV chemotherapy
- Japan Clinical Oncology Group Study JCOG0209 (Ann Oncol. 2014 Jun;25(6):1192-8) – 2 cycles of MVAC

Neoadjuvant chemotherapy continued

- Selected phase 2 NAC trials
 - Accelerated/DD MVAC 3 and 4 cycles (J Clin Oncol.2014 Jun 20;32(18):1895-901 and J Clin Oncol. 2014 Jun 20;32(18):1889-94)
 - 37 (95%) of 39 patients completed all four cycles of chemotherapy
 - Phase 2 NAC GC data with 3-4 cycles (Oncology. 2017;93(1):36-42. doi: 10.1159/000463389. Epub 2017 Apr 12.)
- CER (Cancer 2015 Aug 1;121(15):2586-93).
 - 212 patients (146 patients in the GC cohort and 66 patients in the MVAC cohort) from 28 international centers
 - Comparative effectiveness of GC versus MVAC as NAC for MIBC
 - Median of 3 cycles of NAC
 - pCR rate was 29% in the MVAC cohort and 31% in the GC cohort



Neoadjuvant chemotherapy – cisplatin ineligibility

- “Unfit” criteria - results of a survey of 37 genitourinary medical oncologists (J Clin Oncol. 2011. 29(17) 2432-8).
 - Eastern Cooperative Oncology Group performance status of 2
 - Creatinine clearance less than 60 mL/min
 - Grade \geq 2 hearing loss
 - Grade \geq 2 neuropathy
 - New York Heart Association Class III heart failure
- Consistent with above and similar for CA20927, A031501 and IMvigor010
 - IMvigor010 - Impaired renal function (glomerular filtration rate [GFR] < 60 mL/min); GFR should be assessed by direct measurement (i.e., creatinine clearance or ethyldiaminetetraacetate) or, if not available, by calculation from serum/plasma creatinine (Cockcroft-Gault formula)



Refusing adjuvant treatment as distinct population

- CA20927 - Subjects that are eligible for cisplatin may be candidates if they refuse available adjuvant chemotherapy, despite being informed by the investigator about the treatment options. The subject's refusal must be thoroughly documented
- IMvigor010 - Patients who have not received prior platinum-based neoadjuvant chemotherapy, have refused or are ineligible ("unfit") for cisplatin-based adjuvant chemotherapy
- A031501 - Patients that decline adjuvant cisplatin-based or other systemic chemotherapy based on an informed discussion with the physician and pathologic stage at surgical resection is \geq pT3 or pN+



Refusing adjuvant treatment as distinct population

- Quality of evidence for AC
 - EORTC 30994 (Lancet Oncol. 2015)
 - 284 of planned 660 patients
 - Improvement in PFS (HR 0.54, 95% CI 0.40-0.73; $p < 0.0001$)
 - No significant OS difference (HR 0.78, adjusted 95% CI 0.56–1.08; $p = 0.13$)
 - AC Meta-analysis (Eur Urol. 2014)
 - 945 patients, 9 RCTs
 - For OS, pooled HR 0.77 (95% CI 0.59-0.99; $p = 0.049$)
 - CER (J Clin Oncol. 2015)
 - NCDB (4,360 cystectomy alone vs. 1,293 cystectomy plus AC)
 - OS benefit with AC versus observation
 - HR 0.72 (95% CI 0.67-0.78)



Refusing adjuvant treatment as distinct population

- How much/little do patients understand?
 - *Bad presentation of medical statistics such as the risks associated with a particular intervention can lead to patients making poor decisions on treatment. Particularly confusing are single event probabilities, conditional probabilities (such as sensitivity and specificity), and relative risks. How can doctors improve the presentation of statistical information so that patients can make well informed decisions? (BMJ 2003;327:741)*



Perioperative chemotherapy summary

- How much chemotherapy is sufficient for NAC?
 - 2-3 cycles of cisplatin-based chemotherapy based on randomized phase 3 and selected phase 2 NAC studies?
- Is the consensus definition for cisplatin ineligibility appropriate?
- Is it appropriate to include patients who refuse adjuvant chemotherapy?
 - Level of evidence is less
 - How much/little do patients understand?