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Title: Phase III Trial of Vinflunine (VFL) Plus Best Supportive Care (BSC) After A Platinum-Containing Regimen in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract.

Background:

- Cisplatin based chemotherapy is standard of care for first line management of metastatic urothelial carcinoma (UC); there is currently no standard second line therapy
- Vinflunine (VFL) is a new microtubule inhibitor:
  - Different from other vinca alkaloids because binds relatively weakly to tubulin, suggesting an improved tolerance profile
- VFL activity in metastatic UC had been shown in two previous phase II trials:
  - Culine S et al, Br J Cancer 94: 1395-1401, 2006
  - Vaughn DJ, 2008 ASCO GU Symposium, abs 316

Study design:

- International, multi-centre randomized study (predominantly European)
  - 370 subjects randomized in 83 sites in 21 countries
- Population:
  - Advanced Urothelial Carcinoma, progressed after first line platinum-based regimen
  - PS 0-1
  - Stratified by site and first line platinum refractoriness (defined as refractory if progressed within first two cycles
- Intervention:
  - Patients were randomized in a 2:1 ratio to two arms:
    - **Treatment A: Vinflunine + BSC:**
      - PS 0 = VFL 320 mg/m^2 q3wks
      - PS 1 or previous pelvic radiation = VFL 280 mg/m^2 q3wks, subsequently escalated to 320 mg/m^2 if no hematologic toxicities
    - **Treatment B: BSC**
- Endpoints:
  - Primary: Overall Survival (OS) in intention to treat (ITT) population
    - NB: OS was also calculated for eligible population (post hoc)
    - A multivariate survival analysis was also performed using the prespecified prognostic factors: alk phos, hgb, visceral metastases, PS, lymph node metastases and pelvic radiotherapy
  - Secondary:
    - Progression Free Survival (PFS)

- Disease control rate (DCR) = sum of stable disease + complete and partial responses
- Overall response rate (ORR)
- Clinical benefit: composite of :
  - Performance Status
  - Analgesic consumption
  - Pain index (McGill Pain Questionnaire)
  - Use of palliative radiotherapy
- Quality of Life (QOL):
  - EORTC QOL questionnaire C30

Study results:

- Study groups:
  - Total subjects n=370:
    - 253 were randomized to VFL + BSC
    - 117 were randomized to BSC
- Patient Characteristics:
  - Patient were well balanced with respect to baseline characteristics, except more patients in BSC arm were PS 0: 38.5% vs 28.5%
  - 53% of patients were age <65
  - 32% of patients were PS 0
- Endpoints:

	Treatment A	Treatment B	p-value
1º OS (median)	6.9 mon	4.6 mon	p=0.287
2º PFS	3.0 mon	1.5 mon	**p=0.012**
2º DCR	41.1%	24.8%	**p=0.0024**
2º ORR	8.6%	0%	**p=0.0063**

- Ad hoc analysis on "eligible population":
  - Median OS VFL 6.9 mon vs 4.3 mon, p=0.040
- Multivariate analysis of OS in the ITT population showed a treatment effect on OS:
  - VFL group had a HR for OS of 0.772 (95% CI 0.61-0.98), **p=0.0360**
- Clinical benefit:
  - VFL did not have a negative impact on measures of clinical benefit
  - There was more palliative radiation in BSC group: 24% vs 4% in VFL group
- QOL: VFL did not induce a decrease in health related QOL (p=0.66)
- Toxicities:
  - The VFL group had more myelosuppresion:
    - Grade III/IV neutropenia 50.0%
    - Febrile neutropenia 6.0%
  - Other grade III/IV toxicities common in VFL group:
    - Constipation: 16.1% VFL vs 0.9% BSC
    - Fatigue: 19.3% VFL (17.9% BSC)
    - Abdominal pain: 15.7% VFL (17.9% BSC)

Conclusions:

- While primary endpoint of overall survival in the intention to treat population was not significant, the authors argue this study presents a potentially clinically relevant treatment

Study commentary:

- This is a large (for UC) multinational study:
    - Many phase III trials in UC do not accrue large numbers or are forced to close
- Disappointing results with a negative survival benefit
- VFL is unlikely to become standard second line therapy for UC
- These results, however, do provide some evidence to support second line chemotherapy in platinum-resistant advanced UC

Website link to source: http://jco.ascopubs.org/cgi/content/full/27/27/4454