Oncology Pharmacy Specialty Sessions, Part II

Wednesday, October 19
9:00 a.m.–noon
Convention Center: Rooms 306 & 307

Part of the professional development program for the recertification of board-certified oncology pharmacists, approved by the Board of Pharmacy Specialties and cosponsored by ACCP, the American Society of Health-System Pharmacists (ASHP), and the Hematology/Oncology Pharmacy Association (HOPA). Part I will be presented on Tuesday, October 18, from 1:30 p.m. to 4:30 p.m. Participants must attend all 6 hours of programming to be eligible to complete the Web-based posttest for oncology recertification credit (the posttest must be completed by December 31, 2011). Partial BCOP recertification credit is not available. The posttest fee is $45. After the Annual Meeting, program participants will receive e-mail instructions for accessing the BCOP recertification posttest. Program participants wishing to receive continuing pharmacy education credit will receive an e-mail after the Annual Meeting with instructions about how to claim continuing education credit for these sessions.

Moderator: Ryan N. Bookout, Pharm.D., BCOP
Clinical Pharmacist, Moffitt Cancer Center, Tampa, Florida

9:00 a.m.	Germ Cell Tumors (GCT): Beyond BEP Activity No. 0465-9999-11-402-L04-P *Kellie L. Jones, Pharm.D., BCOP* Clinical Associate Professor, Purdue University School of Pharmacy and Pharmaceutical Sciences, Indianapolis, Indiana
10:00 a.m.	Chronic Lymphocytic Leukemia Activity No. 0465-9999-11-303-L01-P *Ashley K. Morris Engemann, Pharm.D., BCOP* Clinical Associate, Division of Cellular Therapy, Duke University Medical Center, Durham, North Carolina
11:00 a.m.	Updates in the Treatment of Metastatic Breast Cancer Activity No. 0465-9999-11-301-L01-P *Michael J. Berger, Pharm.D., BCOP* Specialty Practice Pharmacist, Arthur G. James Cancer Hospital, Dublin, Ohio

Faculty Conflict of Interest Disclosures

Michael J. Berger: no conflicts to disclose.
Kellie L. Jones: no conflicts to disclose.
Ashley K. Morris Engemann: consulting fees from Genzyme and sanofi Aventis.

Learning Objectives

1. Summarize the current standards of therapy for testicular cancer.
2. Evaluate the impact of stem cell transplant in the metastatic setting.
3. Compare different salvage therapies utilized in the management of metastatic testicular cancer based on efficacy and toxicity.
4. Construct treatment recommendations to manage supportive care issues that testicular cancer patients face during treatment.
5. Outline long-term toxicities associated with the treatment of testicular cancer.
6. Compare and contrast initial treatment strategies for symptomatic or advanced stage chronic lymphocytic leukemia (CLL).
7. Differentiate treatment options for management of relapsed or refractory CLL.
8. Justify the role of allogeneic stem cell transplantation in selected patients with CLL.
9. Discern the role of bevacizumab in the management of patients with metastatic breast cancer (MBC).
10. Compare and contrast targeted therapies for the treatment of $HER2^{(+)}$ MBC.
11. Distinguish chemotherapy treatment options for patients with anthracycline and taxane-refractory MBC based on efficacy and tolerability.
12. Appraise emerging, novel treatment strategies to determine the value of further study and anticipated toxicity profile.

Self-Assessment Questions

Self-assessment questions are available online at *www.accp.com/am*

BCOP RECERTIFICATION

Germ Cell Tumors (GCT): Beyond BEP

Kellie L. Jones, Pharm.D., BCOP
Clinical Associate Professor
Purdue University College of Pharmacy
Salt Lake City, UT

Faculty Disclosure

- Kellie Jones has no areas of conflict to disclose

Objectives

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- Evaluate the impact of stem cell transplant in the metastatic setting.
- Compare different salvage therapies utilized in the management of metastatic testicular cancer based on efficacy and toxicity.
- Construct treatment recommendations to manage supportive care issues that testicular cancer patients face during treatment.
- Outline long-term toxicities associated with the treatment of testicular cancer.

Epidemiology of Testicular Cancer

- 1% of all cancers in men
- Most common carcinoma in men ages 15-35
- Estimated 8,480 cases in 2010
  - 350 estimated deaths
- Goal of therapy is cure
  - ~ 60% present with localized disease
  - ~ 15% present with metastatic disease
- Seminoma or non-seminoma GCT's

Jemal A, et al. *CA Cancer J Clin.* 2010;60:277-300.

Histology of Testicular Cancer

- Seminoma
  - Does not secrete alpha fetoprotein (AFP)
- Non-seminoma
  - Can secrete AFP and/or beta human chorionic gonadotropin (β-HCG)
  - Embryonal
  - Yolk sac
  - Choriocarcinoma
  - Teratoma

False elevations may occur with:
Liver cancer
Hepatitis/cirrhosis
Alcohol abuse
Marijuana use

International Germ Cell Cancer Collaborative Group (IGCCG) Risk Classification

Risk Status	Non-Seminoma	Seminoma
Good risk	Testicular or retroperitoneal primary No non-pulmonary mets **AFP < 1,000 ng/mL** **hCG < 5, 000 IU/L** **LDH < 1.5 x ULN**	Any site, no non-pulmonary mets **Normal AFP** **Any hCG** **Any LDH**
Intermediate risk	Same as above with: **AFP 1,000-10,000 ng/mL** **hCG 5,000-50,000 IU/L** **LDH 1.5-10 x ULN**	Same as above, with non-pulmonary visceral metastases
Poor risk	Non-pulmonary visceral metastases present (i.e. bone, liver, brain): **AFP > 10,000 ng/mL** **hCG > 50,000 IU/L** **LDH < 10 x ULN**	No patients classified as poor risk

Reprinted with permission from the American Society of Clinical Oncology. *J Clin Oncol.* 1997;15:594-603.

Staging

- Stage I
  - Confined to the testes
- Stage II
  - Involves the testes and the retroperitoneal and/or para-aortic lymph nodes
- Stage III
  - Spread beyond the retroperitoneal lymph nodes
  - Can spread to lymph nodes, lungs, brain, and liver

Treatment Based on Stage

Stage	Histology	Treatment modality
1	Seminoma	Radiation
		Observation
		Chemotherapy
	Non-seminoma	Surgery (RPLND)
		Chemotherapy
		Observation
2	Seminoma	Radiation
		Chemotherapy
	Non-seminoma	Surgery (RPLND)
		Chemotherapy
3	Seminoma	Chemotherapy
	Non-seminoma	Chemotherapy

Adapted from NCCN Guidelines. Testicular Cancer v.2.2010.

Question # 1

Which of the following is the standard treatment for good risk testicular cancer?

1. Bleomycin, epirubicin, prednisone
2. Busulfan, etoposide, cisplatin
3. Bleomycin, etoposide, cisplatin
4. Busulfan, epirubicin, paclitaxel

Management of Good Risk Disease

- BEP x 3 = BEP x 4 (SECSG)[1]
- BEP x 3 superior to EP x 3 (ECOG)[2]
- BEP x 3 = EP x 4 (EORTC)[3]
- BEP superior to BE + (Carboplatin) (EORTC)[4]
- EP x 4 superior to E + (Carboplatin) (Memorial)[5]

BEP x 3 standard of care for good risk patients with > 90% cure rate

B = Bleomycin, E = Etoposide, P = Cisplatin; SECSG = South East Cancer Study Group;
ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer.

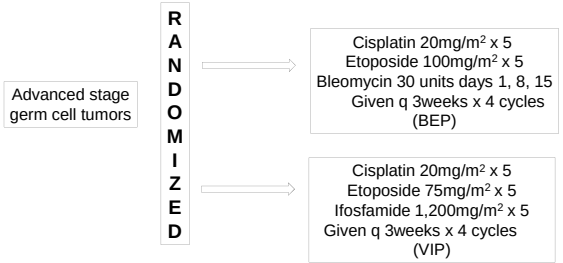
1. Einhorn LH, et al. J Clin Oncol. 1989; 7:387-91; 2. Loehrer PJ, et al. J Clin Oncol. 1995;13:470-6;
3. de Wit R, et al. J Clin Oncol. 1997;15:1837-43; 4. Horwich A, et al. Proc Am Soc Clin Oncol. 1994; 13:230.;
5. Bajorin DF, et al. J Clin Oncol. 1993;11:598-606.

Poor Risk Disease

- Advanced disease
- Cure rate 40-60%
- Goal of therapy:
  - Improve on the current cure rate
  - Improve upon the standard BEP x 4 regimen
    - Use of different regimens such as VIP

VIP = Etoposide, Ifosfamide, and cisplatin

Poor Risk Disease



Hinton S, et al. *Cancer.* 2003;97(8):1869-75.

Slide 10

"HP3 use = here as in bullet 3

KJ: OK
"Clarian Health Partners, 11/11/2010

Poor Risk Disease Results

Response (%)	BEP x 4 (n= 141)	VIP x 4 (n = 145)	P value
CR	31	37	NS
PFS	58	64	NS
OS	67	69	NS
Toxicities (%)	**BEP x 4**	**VIP x 4**	
Overall toxicities*	79	93	P = 0.0002
Hematologic♥	76	90	P = 0.003

*Overall toxicities included: Nausea/vomiting, infection, bleeding, neurologic, respiratory, genitourinary, hepatic, and hematologic; ♥Hematologic toxicity was most common toxicity no matter the treatment arm

Hinton S, et al. *Cancer.*2003;97(8):1869-75.
CR = Complete response; PFS = Progression free survival; OS = overall survival; NS = non-significant

Poor Risk Disease

- Toxicities
  - Increased with VIP
  - Because of this, BEP is standard of care
- VIP used to prevent pulmonary toxicities
  - Extensive mediastinal disease
  - Underlying pulmonary dysfunction

Post Treatment Resection

- Should be conducted on residual retroperitoneal masses
- RPLND should be considered in larger, persistent masses
  - Only by highly skilled surgeon
- Masses can comprise:
  - Necrosis, teratoma, malignant germ cells
  - Teratomas can transform to sarcoma

Oldenburg J, et al. *J Clin Oncol.*2006;24:5503-11.

RPLND: Retroperitoneal lymph node dissection

Post Treatment Follow Up

Type	Tests	Interval
Seminoma	Tumor Markers	1st year: q 2 - 4 months 2nd year: q 3 - 4 months 3rd - 4th year: q 4 - 6 months Annually thereafter
	Abdominal CT Scans	1. Annually if para-aortic radiotherapy 2. At each visit alternating with chest x-ray for up to 10 years
Non-seminoma	Tumor Markers	1st year: q 1- 2 months 2nd year: q 2 - 4 months 3rd - 4th year: q 3 - 6 months 5th year: q 6 months Annually thereafter
	Abdominal CT Scans	1st year: q 6 months 2nd year: q 6 - 12 months Annually up to 5 years, then as indicated

Gilligan TD, et al. *J Clin Oncol.* 2010;28:3388-3404.
NCCN Clinical Practice Guidelines in Oncology; Testicular Cancer. V2.2010.

Post Treatment Follow Up

- After surgery and chemotherapy, tumor markers should ↓
  - AFP serum half life = 5 - 7 days
  - β-HCG serum half life = 18 - 36 hours
  - A plateau or slow decline suggests residual active disease

The Most Curable Metastatic Cancer

- Testicular cancer
- Second most curable cancer:
  - Second line therapy for testicular cancer
- Third most curable cancer:
  - Third line therapy for testicular cancer

Question # 2

Which of the following is the best answer regarding the use of high dose chemotherapy and stem cell transplant in testicular cancer?

1. High dose chemotherapy with stem cell transplant prolongs DFS, but not OS.
2. Tandem stem cell transplant is standard of care for recurrent disease.
3. Induction chemotherapy prior to stem cell transplant includes VIP for 2 cycles.
4. Stem cell transplant is considered after failing 2 salvage chemotherapy regimens

Prognostic Factors for Salvage Conventional Dose Chemotherapy (CDC)

Up to 70% who relapse or fail to achieve a CR can be cured

Good prognostic factors:
- Testis or retroperitoneal primary site and CR to initial therapy
- 35 - 40% 3 year survival with CDC

Poor prognostic factor:
- Incomplete response to initial therapy or relapsed mediastinal NSGCT
- < 10% 3 year survival with CDC

Bosl GJ. Cancer of the Testis. In: DeVita VT Jr. Cancer: Principles & Practices of Oncology. 2008:1463-85.
NSGCT = Non-seminomatous germ cell tumor

Prognostic Factors for High Dose Chemotherapy (HDC)

- Those less likely to benefit from HDC:
  - Primary mediastinal GCT refractory to initial and salvage chemotherapy
  - Refractory disease
    - Rising markers or radiographic evidence of progression within 4 weeks of cisplatin
    - High β-HCG levels (> 1,000 IU/L)

Bosl GJ. Cancer of the Testis. In: DeVita VT Jr. Cancer: Principles & Practices of Oncology. 2008:1463-85.
Einhorn LH, et al. NEJM. 2007; 357:340-8.

The case for HDC

- Poor risk patients do not have the same high rate of cure as good/intermediate risk (50%)
- GCT's are highly responsive to chemo
- High dose chemo as 3rd line salvage therapy
  - 10 - 20% cure rate
- Improved supportive care
- Patient's age permits use of high dose chemotherapy with improved safety profile

History of High Dose Chemotherapy

1986 Phase I/II trial: 2 cycles of HDC with carboplatin/etoposide
- Nichols CR, et al. *J Clin Oncol.*1989;7:932-9.

⇩

1997 2 cycles of HDC with carboplatin/etoposide
- Broun ER, et al. *J Clin Oncol.*1997;79:1605-10.

⇩

2000 Review of 65 patients with HDC at Indiana University Hospital
- Bhatia S, et al. *J Clin Oncol.*2000;18:3346-51.

⇩

2000 High dose carboplatin/etoposide/cyclophosphamide in poor risk patients
- Motzer RJ, et al. *J Clin Oncol.*2000;15:2546-52.

⇩

2007 Review of 184 patients with HDC with carboplatin and etoposide at Indiana University Hospital (2nd and 3rd line results)
- Einhorn LH, et al. *NEJM.* 2007;18:3346-51.

High Dose Chemotherapy (HDC)

- Retrospective review of 184 patients with cisplatin-resistant, progressive GCT's
- VeIP x 2 cycles ⇒ HDC (n = 173)
- VeIP x 1 cycle ⇒ HDC (n = 11)
- Primary endpoint
  - Disease Free Survival
- Secondary endpoint
  - Overall survival

VeIP =	Vinblastine	0.11 mg/kg IV on days 1, 2
	Ifosfamide	1200 mg/m^2 IV on days 1-5
	Cisplatin	20 mg/m^2 IV on days 1-5

Einhorn LH, et al. *NEJM.* 2007;357:340-8.

Patient Characteristics

Patient Characteristics	Number of patients (%)
# of previous chemo regimens	
1	135 (73.4)
2	45 (24.4)
3	4 (2.2)
Response to initial chemotherapy	
CR	75 (40.8)
PR	9 (4.9)
< CR or PR with normal tumor markers	100 (54.3)
Initial IGCCCG stage (risk)	
Low	71 (38.6)
Intermediate	38 (20.7)
High	75 (40.8)

Einhorn LH, et al. *NEJM.* 2007;357:340-8.

CR = complete remission; PR = partial remission

High Dose Chemotherapy

- HDC consisted of:
  - Carboplatin 700 mg/m^2 on days -5, -4, -3
  - Etoposide 750 mg/m^2 on days -5, -4, -3
- ≥ 1 million CD34+ cells/kg were required for each cycle of HDC
- No planned reductions/escalations of doses
- 2nd cycle given after recovery of counts, unless toxicities (grade 4 non-hematologic), or no response to the 1st cycle

Einhorn LH, et al. *NEJM.* 2007;357:340-8.

HDC - Treatment Schema

Mobilization of peripheral blood stem cells (PBSC): G-SCF (10 µg / kg / d)

↓

Apheresis (adequate number for 2 autologous transplants)

↓

Cycle 1 high dose chemotherapy:
Carboplatin days -5, -4, -3
Etoposide days -5, -4, -3

↓

PBSC re-infusion day 0 and Filgrastim starting day 0

↓

Perform additional mobilization and PBSC collection if needed

↓

Cycle 2 high dose chemotherapy as given in cycle 1

Bhatia S, et al. *J Clin Oncol.* 2000;18:3346-51; Einhorn LH, et al. *NEJM.* 2007;357:340-8.

Results

- 40/184 (22%) were platinum refractory
- 116/184 (63%) were disease free at a median follow-up of 48 months
  - 104/116 (90%) were disease free > 2 years
- 6 patients = CR
  - 4 patients = CR after paclitaxel + gemcitabine
  - 2 patients = CR after resection

Einhorn LH, et al. *NEJM.* 2007;357:340-8.

Results – Disease Free Survival

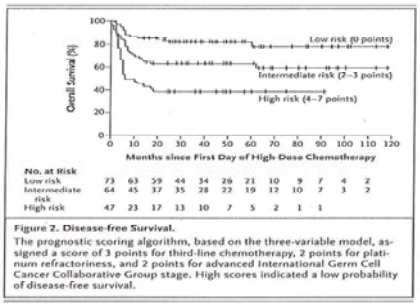


Figure 2. Disease-free Survival.
The prognostic scoring algorithm, based on the three-variable model, assigned a score of 3 points for third-line chemotherapy, 2 points for platinum refractoriness, and 2 points for advanced International Germ Cell Cancer Collaborative Group stage. High scores indicated a low probability of disease-free survival.

Einhorn LH, et al. *NEJM.* 2007;357:340-8.

Results

- Prognostic variables associated with statistical improvement in PFS
  - HDC as 2nd line therapy vs. 3rd line
  - Platinum sensitivity
  - Response to initial chemotherapy
  - Favorable prognosis
  - Favorable IGCCCG score

Einhorn LH, et al. *NEJM.* 2007;357:340-8.

Grade 3 and Higher Toxicities

Total patients = 184	Number of patients
Hematologic (leukemia)	3
Renal (creatinine ↑'d 3-6 x ULN)	4
Gastrointestinal	30
Hepatic	6
Neurologic	9
Pulmonary	3

2 deaths were associated with leukemia
2 deaths were associated with hepatic dysfunction
1 death was associated with pulmonary toxicities

HDC with PBSCT can cure metastatic GCT's when used as 2nd line and even as 3rd line therapy

Einhorn LH, et al. *NEJM.* 2007;357:340-8.

ULN = Upper limit of normal

HDC – Supportive Care- Prophylaxis Indiana University

Start on:	Day -1	Day 0
Ciprofloxacin 500 mg po BID	X	
Fluconazole 400 mg po daily	X	
Acyclovir 400 mg po BID	X	
Vancomycin 1500 mg IV Q12 hours	X	
Use once daily in outpatient		
Filgrastim subcutaneously daily		X
Stop: ANC is = or > 2000/mm^3 x 2 days Stop: ANC = or > 10,000/mm^3 x 1 day		
Adequate hydration		

Tomblyn M, et al. Biol Blood Marrow Transplant. 2009;15:1143-1238; Bhatia S, et al. J Clin Oncol. 2000. 18:3346-3351; Broun ER, et al. Antimicrob Agents Chemother. 1994;38(3):576-579.

HDC – Supportive Care - Antiemetics

- ASCO Guidelines: Stem Cell Transplant
  - Highly emetogenic regimen
    - 5-HT$_3$ serotonin receptor antagonist
    - Dexamethasone
    - Aprepitant
      - Should be considered although evidence to support its use specifically in these patients is lacking
- NCCN Guidelines: Stem Cell Transplant
  - Aprepitant may be used for multiple day regimens. Based on phase II data, the drug has been safely given on days 4 and 5

NCCN. Antiemetic guidelines v.1.2011; Kris MG, et al. J Clin Oncol. 2006;24:2932-47.

HDC – Supportive Care- Antiemetics Indiana University

Day	- 5	- 4	- 3	- 2	- 1	0
Aprepitant 125 mg po	X					
Aprepitant 80 mg po		X	X	X	X	
Ondansetron 24 mg po	X	X	X			
Dexamethasone 12 mg po	X	X	X			
Dexamethasone 8 mg po				X	X	X
Lorazepam 1mg IV/PO q 4 hour PRN						

Maintenance Etoposide

- Maintenance oral etoposide
  - Platinum refractory, high risk disease
  - 50 mg/m^2 daily every 3 weeks, with 1 week off
    - Repeat x 3 cycles

Saxman S. *Drugs.* 1999;58(3):31-34.

HDC vs. CDC

- Retrospective review of 1,594 patients
  - 773 received conventional chemotherapy
  - 821 received HDC
- Evaluated use of second line therapy in patients who received prior cisplatin
- Patients were classified according to risk:
  - Very low, low, intermediate, high, very high
- Estimated 2 year PFS and 5 year OS

Lorch A, et al. *J Clin Oncol.* 2010;28:15S:4513.

HDC vs. CDC

(Number of patients)	2 yr PFS (%)	5 yr OS (%)
All patients (1594) HDC vs. CDC	49.6 vs. 27.8 P < 0.001	53.2 vs. 40.8 P < 0.001
Very low risk (76) HDC vs. CDC	91.6 vs. 58.4 P < 0.008	88.7 vs. 64.5 P < 0.007
Low risk (257) HDC vs. CDC	64.3 vs. 40 P < 0.001	64.5 vs. 66.2 P = 0.901
Intermediate risk (546) HDC vs. CDC	53.5 vs. 31.9 P < 0.001	58.3 vs. 45.5 P < 0.002
High risk (351) HDC vs. CDC	33.3 vs. 17.2 P < 0.001	35.2 vs. 23 P < 0.001
Very high risk (105) HDC vs. CDC	22 vs. 1.9 P < 0.001	27 vs. 3.4 P < 0.002

Lorch A, et al. *J Clin Oncol.* 2010;28:15S:4513.

Question # 3

Which of the following is the most effective salvage chemotherapy regimen for patients with recurrent disease?

1. TIP
2. Etoposide
3. PVB
4. VeIP

Salvage Chemotherapy - VeIP

- Vinblastine, Ifosfamide, and Cisplatin
  - 135 patients who progressed on cisplatin based chemotherapy
  - Included both gonadal (n=100) and extragonadal tumors (n=35)
- Patients received VeIP every 3 weeks x 4

VeIP =	**Vinblastine**	0.11 mg/kg IV on days 1, 2
	Ifosfamide	1200 mg/m^2 IV on days 1-5
	Cisplatin	20 mg/m^2 IV on days 1-5

Loehrer PJ, et al. *J Clin Oncol.*1998;15:2500-04.

Salvage Chemotherapy - VeIP

- 67 (50%) achieved a CR after chemotherapy with or without surgery
- 42 (32%) were alive at 6 years
- 32 (24%) were NED at 6 years
  - No patients with extragonadal tumors were NED compared to 30% of testicular primaries

Loehrer PJ, et al. *J Clin Oncol.* 1998;15:2500-04.

NED = No evidence of disease

Salvage Chemotherapy - TIP

- Paclitaxel, Ifosfamide, and Cisplatin (TIP)
  - 46 patients previously treated and prior CR
  - Gonadal primaries
- Patients received TIP every 3 weeks x 4

Paclitaxel	250 mg/m^2 continuous IV on day 1
Ifosfamide	1500 mg/m^2 IV on days 2-5
Cisplatin	25 mg/m^2 IV on days 2-5
Mesna	1500 mg/m^2 IV on days 2-5

- All patients received colony stimulating agents

Kondagunta GV, et al. *J Clin Oncol.*2005;23:6549-55.

Salvage Chemotherapy - TIP

- 32 patients (70%) achieved a CR
- 29 patients (63%) achieved a CR at the follow up of 69 months
  - Continue to be NED at 5 years
- 7 of 14 patients with late relapse disease achieved a CR with chemotherapy followed by surgical resection
- Toxicities:
  - 48% admission for neutropenic fever

Kondagunta GV, et al. *J Clin Oncol.*2005;23:6549-55.

Other Salvage Chemotherapy

- So why use paclitaxel plus gemcitabine?
  - Single agent paclitaxel results: 11-26%
  - Single agent gemcitabine results: 19-20%
- Review of 32 patients that had progressed after receiving HDC (platinum refractory)

Paclitaxel	100 mg/m^2 IV over 1 hour
Gemcitabine	1000 mg/m^2 IV over 30 minutes days 1, 8, 15 every 28 days

Einhorn, LH, et al. *J Clin Oncol.* 2007;25:513-16.

Paclitaxel + Gemcitabine

- 25 received therapy as 3rd line, with 6 patients receiving therapy as 4th line
- Main toxicities: Myelosuppression and neuropathy
- Results:
  - 4 partial remissions (for 2 - 6 months)
  - 6 complete responses
    - 4 of those 6 continued to be NED at 20, 40, 44, and 57 months, respectively

Einhorn, LH, et al. *J Clin Oncol.* 2007;25:513-16.

Other Salvage Chemotherapy

Regimen	# pts	Results	
		RR (%)	CR (#)
Oxaliplatin	32	13	
Oxaliplatin + gemcitabine	35		3
Oxaliplatin + gemcitabine	28		4
Irinotecan + platinum	18		2
Oxaliplatin + irinotecan	18		3
Cisplatin + epirubicin	30		9

Sonpavde G, et al. *The Oncologist.*2007;12:51-61.
Bedano P, et al. *J Clin Oncol.*2006;24:5403-07.

RR = Response rate; CR = Complete remission

Other Salvage Chemotherapy

- Etoposide
  - Phase II trial in refractory tumors (N = 22)
    - 50 mg/m^2 orally rounded to nearest 25 mg
      - 3 = Partial response
      - 8 = Stable disease

Cooper M, et al. *J Clin Oncol.*1995;13:1167-9.

Other Salvage Chemotherapy

- Maintenance after salvage therapy (N = 34)
  - Median prior regimens = 2
  - 14 received previous stem cell transplant
  - 50 mg/m^2/day orally for 21 days
    - Repeat every 28 days x 3 cycles
  - Prior to maintenance therapy:
    - 11 patients achieved PR and 23 patients achieved CR
  - 17 of 23 patients maintained CR with no evidence of recurrence at a median follow-up of 36 months
  - Less toxicities than with continuous administration
  - Neutropenia, mucositis, and neutropenic fever

Saxman S. *Drugs.*1999;58(3):31-34.

Supportive Care Issues in GCTs

- Short term toxicities
  - Nausea/vomiting
  - Pain management
  - Febrile neutropenia
  - Testosterone deficiency

Question # 4

Which of the following is a common short-term toxicity associated with testicular cancer chemotherapy?

1. Leukemia
2. Mucositis
3. Pneumonitis
4. Nausea/vomiting

Supportive Care Issues in GCTs

- Nausea/vomiting
  - Highly emetogenic regimens
  - Prophylaxis with 3 drug regimen as per ASCO/NCCN guidelines
    - 5-HT_3 antagonist, dexamethasone, aprepitant
  - Adequate hydration

Supportive Care Issues in GCTs

- Pain Management
  - Initially patients may have increased pain
    - Lower back, abdominal, post-surgical site
  - Pain dramatically ↓'s with chemotherapy

Supportive Care Issues in GCTs

- Testosterone Deficiency
  - No standard treatment/follow - up guidelines
  - Many patients will maintain normal testosterone levels
  - Testosterone levels can be tested when patient experiences symptoms:
    - Loss of libido, fatigue, increased sweating, impotence
    - Check testosterone level early in morning
      - (i.e. 7:00 – 8:00 am)

Mulder JE. *Med Ped Oncol.*1999;33:46-52; Carnegie C. *Rev Urol.* 2004;6(suppl 6);S3-S8.

Supportive Care Issues in GCTs

- Testosterone Deficiency
  - Maintain physiologic testosterone range
    - 280-800 ng/dL and monitor every 3 to 4 months
  - Many formulations of testosterone replacement
    - Topical gel, transdermal patches, injections
- Survey of testicular cancer survivors (n = 83)
  - 25% of patients experienced hypogonadism
  - Symptoms of androgen deficiency were not associated with testosterone levels
    - Sexual dysfunction, chronic fatigue

Petak SM, et al. *Endocr Pract.* 2002;8(6):439-456; Lackner JE, et al. *J Urol.* 2009;74:825-830.

Question # 5

Which of the following would be considered a long-term toxicity of testicular cancer treatment?

1. Pain management
2. Nephrotoxicity
3. Neutropenic fever
4. Electrolyte imbalances

Long Term Toxicities

- Sterility
- Neuropathy
- Nephrotoxicity
- Pulmonary toxicity
- Tinnitus
- Vascular toxicities
- Secondary malignancies
- Late relapse

Toxicities that persist >12 months or that are present 12 months after the end of therapy

Long Term Toxicities

- Sterility
  - At time of diagnosis 10 - 35% are infertile
  - Reasons induce:
    - Abdominal radiotherapy, RPLND, chemotherapy
  - ↑'s in FSH and LH up to 2 years after therapy
  - ↓'d testosterone leads to worsening sexual function, psychosocial functioning, increased BMI and blood pressure

RPLND = Retroperitoneal lymph node dissection; FSH = follicle stimulating hormone; LH = Luteinizing hormone; BMI = Body mss index

Long Term Toxicities

- Sterility (continued):
  - Likelihood of fathering a child after therapy for testicular cancer
    - Chemotherapy = 71%
    - Chemotherapy + Radiation = 67%
  - Risk factors for azoospermia:
    - Radiation therapy
    - Age > 30 years
    - Chemotherapy duration > 6 months
- SPERM BANKING DISCUSSION!!!!

Pliarchopoupou K, et al. *Cancer Treat Rev.* 2010; 36:262-67.

Long Term Toxicities

- Neuropathy
  - Cisplatin
    - Numbness and tingling
  - Vinblastine
    - "Stocking glove"
  - Can occur in up to 80% of patients
  - Can persist after therapy (up to 50%)

Hansen SW, et al. *J Clin Oncol.*1989;7:1457.

Long Term Toxicities

- Nephrotoxicity: Cisplatin
  - ↓'s in glomerular filtration rate and electrolyte disturbances from tubular dysfunction
  - Damage to proximal tubules: magnesium wasting
- Can be reversible or irreversible and may last > 12 months
- Adequate hydration for prevention
- Risk factors:
  - Total cisplatin dose, other concomitant nephrotoxic agents, pre-existing renal disease

Pliarchopoupou K, et al. *Cancer Treat Rev.* 2010; 36:262-67.

Long Term Toxicities

- Pulmonary: **BLEOMYCIN**
  - Risk factors:
    - Cigarette smoking, radiation, cumulative bleomycin dose (~ 9% in doses > 300 units)
    - Prior surgery (or intubation), exposure to high concentrations of oxygen
  - Patients may experience:
    - Bronchiolitis obliterans or interstitial pneumonitis
  - Long-term pulmonary function is preserved in most, but the toxicity can persist in others

Pliarchopoupou K, et al. *Cancer Treat Rev.* 2010; 36:262-67.

Long Term Toxicities

- Pulmonary: **BLEOMYCIN**
  - Stop bleomycin therapy!
  - Administer steroids for symptomatic relief
  - Physical assessment prior to each dose of bleomycin should occur to assess changes
  - Pulmonary function tests can be ordered and followed; however do not always predict lung damage

Sleijfer S. Chest. 2001;120:617-24.

Long Term Toxicities

- Tinnitus
  - High frequency hearing loss (4 to 8 MHz)
  - Persistent problems ~ 20% of patients
- Vascular toxicities
  - Raynaud's
    - Bleomycin can cause this
    - Up to 50% of patients experience toxicity
    - Can persist for years after therapy
    - ?? related to cisplatin hypomagnesemia

Vaughn DJ, et al. *Ann Intern Med.*2002;136;463-70; Soble AR. *Cancer Treat Rep.*1978; 62:570.

Cardiovascular Complications

- Myocardial infarction
- Thromboembolic disease
- Hyperlipidemia
- Hypertension
- Stroke
- Metabolic Syndrome
- Increased BMI

- 2 x ↑'s of CV risk compared to general population
- Endothelial cell damage
  - Microalbuminuria
- Indirect effects
  - Can be related to hormonal effects (↓'d testosterone)
- Metabolic syndrome
  - 25 - 40% vs. 3 - 4% in general population

Meinardi MT, et al. *J Clin Oncol.*2000;18(8):1725-32; Haugnes HS, et al. *Ann Oncol.* 2007;18(2):241-8.

Cardiovascular Risk- 20 year follow-up

- 990 men in 20 year follow-up study
- 4 treatment groups
  - Surgery (n = 206)
  - Radiotherapy alone (n = 386)
  - Chemotherapy alone (n = 264)
  - Radiotherapy + chemotherapy (n = 34)
    - Anti-hypertensive use was highest:
      - – Chemotherapy alone arm

Haugnes HS, et al. J Clin Oncol. 2010; 28:4649-4657.

Cardiovascular Risk- 20 year follow-up

Event	HR	95% CI
Coronary Artery Disease		
RT	2.1	0.78 - 5.5
Chemotherapy	2.6	0.96 - 6.9
RT + Chemotherapy	5.3	1.5 - 18.5
Myocardial Infarction		
Chemotherapy (BEP)	3.1	1.2 - 7.7
RT + Chemotherapy	4.8	1.6 - 13.9

Haugnes HS, et al. J Clin Oncol. 2010; 28:4649-4657.
Radiation therapy; HR = Hazard ratio, CI = Confidence Interval.

Secondary Malignancies

- Cancer registry of 28,843 testicular cancer patients demonstrated increased risk:
  - Observed to expected ratio:
    - 1.43 (CI, 1.36-1.51)
- Risk ↑'s with chemotherapy or radiation

Secondary Malignancies Associated After Therapy	
Testicular (contralateral)	Pleura
Pancreas	Stomach
Bladder	Connective tissue
Myelodysplastic syndrome	Leukemia

Travis LB, et al. *J Natl Cancer Instit.*1997;89:1429-39; Piliarchopoupou K, et al. *Cancer Treat Rev.*2010;36:262-67.

Secondary Malignancies

- Leukemia
  - Etoposide
    - Doses > 2 grams/m^2, total dose, schedule
  - Relative risk within 10 years: 3 - 7%
- Retrospective review of 113 pts after HDC
  - Risk of leukemia ↑'d by 2.6% with etoposide
- NCI Cancer Therapy Evaluation Program
  - 6 year rate of leukemia: 0.7 - 3.2% after etoposide therapy

Piliarchopoupou K, et al. *Cancer Treat Rev.*2010;36:262-67.; Vaughn DJ, et al. *Ann Intern Med.* 2002;136:463-70. Houck W, et al. *J Clin Oncol.* 2004;22:2155-58. NCI = National Cancer Institute

Secondary Malignancies: ASCO 2010

- Horwich A. 2010;28:15s:4538
  - 2,703 patients: Infradiaphragmatic radiotherapy
  - Primary outcome: # of secondary cancers
    - 18 year follow-up demonstrated increased rates of:
      - Stomach, pancreas, and bladder cancers
- Lewinshtein C. 2010;28:15s:4537
  - Retrospective: SEER database (1973-2006)

Total patients = 20,300	Leukemia/Lymphoma	Bladder Cancer
All patients (n)	139	99
Radiotherapy (n)	76	56

Late Relapse

- One of the most challenging dilemmas
- Defined as recurring 2 years or later after successful treatment
- Very rare: 1 - 3%
- Predominate site of relapse:
  - Retroperitoneum and chest
- Surgery is mainstay of therapy
  - Often refractory to chemotherapy

Oldenburg J, et al. *J Clin Oncol.*2006;24:5503-11; Vaughn DJ, et al. *Ann Intern Med.* 2002;136:463-70.

Late Relapse

- Seminomas
  - Those on surveillance are cured by radiation therapy, cisplatin based chemotherapy, or surgery
- Non-seminomas
  - Surgery is considered the mainstay in patients that have already received chemotherapy

What to do when there is no drug?

- Everyone is dealing with national shortages
- All drugs affected
- What do you do?
  - Delay treatment?
    - **Not an option**
  - Transplant?
    - High dose etoposide (if you can get it)
  - Bring out the old regimens!!

Other Chemotherapy Options

- Good risk patients (PVB)

Cisplatin	20 mg/m^2 IV on days 1-5
Vinblastine	0.20 mg/kg IV days 1, 2
Bleomycin	30 units IV on day 2

- Poor risk disease (VeIP)

Vinblastine	0.11 mg/kg IV on days 1, 2
Ifosfamide	1200 mg/m^2 IV on days 1-5
Cisplatin	20 mg/m^2 IV on days 1-5

Conclusions

- Testicular cancer is a very curable disease
- If a patient recurs, cure is still an option
- HDC followed by stem cell transplant is an option for 2nd line therapy and offers cure
- Salvage regimens such as VeIP, TIP, paclitaxel + gemcitabine have been used
- An understanding of short-term and long-term toxicities is important

BCOP RECERTIFICATION

Germ Cell Tumors (GCT): Beyond BEP

Kellie L. Jones, Pharm.D., BCOP
Clinical Associate Professor
Purdue University College of Pharmacy
Salt Lake City, UT

BCOP RECERTIFICATION

Chronic Lymphocytic Leukemia: Treatment Update

Ashley Morris Engemann, Pharm.D., BCOP
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Duke University Medical Center

Faculty Disclosure

- Ashley Morris Engemann has received consulting fees from Genzyme and Sanofi Aventis

Learning Objectives

- Compare and contrast initial treatment strategies for symptomatic or advanced stage chronic lymphocytic leukemia (CLL).
- Differentiate treatment options for management of relapsed or refractory CLL.
- Justify the role of allogeneic stem cell transplantation in selected patients with CLL.

Epidemiology and Natural History

- 15,000 new cases in US annually
- 4,400 deaths in US annually
- Median age at diagnosis 65-70 years
- May initially be asymptomatic (25%)
- Symptoms increase with disease progression
- Incurable with conventional chemotherapy

Cancer Facts and Figures 2010. Atlanta: American Cancer Society; 2010.
Seung AH. Am J Health-Syst Pharm 2010;67:1813-24.

Prognostic Factors

- Favorable
  - Early stage or low risk
  - Immunoglobulin Variable Region (IgV_H)
    - > 2% mutation
  - Del(13q) as sole abnormality; median survival 133 months
- Unfavorable
  - Advanced stage or high risk
  - CD38 (if >= 30%)
  - Zeta-associated protein 70 (ZAP 70) (if >= 20%)
  - Del(11q); median survival 79 months
  - Del(17p); median survival 32 months

Damle RN, et al. Blood 1999;94:1840-7. Crespo M, et al. N Engl J Med 2003;348:1764-75.
Wiestner A, et al. Blood 2003;101:4944-51. Seung AH. Am J Health-Syst Pharm 2010;67:1813-24.

First-Line Therapy

Audience Response Question

1. Initiation of treatment is recommended for which of the following patients with CLL?
   A. All patients regardless of stage
   B. All patients with high risk features regardless of stage
   C. Only patients with significant disease-related symptoms
   D. Patients with Rai Stage III or IV disease only

Active Surveillance

- Recommended for
  - Rai Stage 0 (low risk)
  - Rai Stage I-II (intermediate risk)
- Early treatment in asymptomatic patients
  - May improve progression-free survival
  - Has no impact on overall survival
- Remains an active area of research
  - Primary focus on high-risk disease

NCCN. Non-Hodgkin's Lymphomas. v.1.2011. Available at: www.nccn.org/professionals/physician_gls/PDF/nhl.pdf
Brugiatelli M, et al. Eur J Haematol 1995;55(3):158-63. The French Cooperative Group on CLL. Blood 1990;75(7):1414-21.
Mhaskar AR, et al. Cancer Treat Rev 2010;36:621-8.

Indications for Treatment

- Significant disease-related symptoms
  - Night sweats
  - Fatigue
  - Weight loss
  - Fever without infection
- Progressive bulky disease
- Lymphocyte doubling time <= 6 months

NCCN. Non-Hodgkin's Lymphomas. v.1.2011. Available at: www.nccn.org/professionals/physician_gls/PDF/nhl.pdf

Indications for Treatment (continued)

- Progressive anemia or thrombocytopenia
- Threatened end-organ function
- Absolute lymphocyte count >200,000-300,000 x 10^9/L or symptoms related to leukostasis
- Eligible for clinical trial

NCCN. Non-Hodgkin's Lymphomas. v.1.2011. Available at: www.nccn.org/professionals/physician_gls/PDF/nhl.pdf

Audience Response Question

2. At your institution, what is the preferred first-line regimen for standard-risk CLL patients less than 70 years of age?
   A. Fludarabine, cyclophosphamide, rituximab (FCR)
   B. Bendamustine, rituximab (BR)
   C. Pentostatin, cyclophosphamide, rituximab (PCR)
   D. Alemtuzumab
   E. Other

First-Line Treatment: Chlorambucil versus Fludarabine

Study	Endpoint	Fludarabine	Chlorambucil	p value
Rai 2000 (C9011)	ORR	63%	37%	<0.001
n=509	CR	20%	4%	<0.001
(F=170/C=181)	PFS	20 months	14 months	<0.001
Last f/u 1999	OS	66 months	56 months	NS
Rai 2009 (C9011)	OS	63 months	59 months	0.04
N=509	Alive at 4 yrs	60%	60%	
Last f/u 2009	Alive at 6 yrs	43%	38%	
	Alive at 8 yrs	31%	19%	

Fludarabine 25 mg/m^2 IV daily x 5 days q28d
Chlorambucil 40 mg/m^2 PO once q28d

Rai KR, et al. N Engl J Med 2000;343:1750-7. Rai KR, et al. Blood 2009;114: Abstract 536.

First-Line Treatment: Chlorambucil versus Fludarabine

Study	Endpoint	Fludarabine	Chlorambucil	p value
Catovsky 2007	ORR	80%	72%	0.04
N=777	CR	15%	7%	0.006
	PFS	20 months	23 months	0.1
	5-yr OS	52%	59%	0.2
Eichhorst 2009	ORR	72%	51%	0.003
n=193	CR	7%	0%	0.011
	PFS	19 months	18 months	0.7
	OS	46 months	64 months	0.15

Eichhorst: Fludarabine 25 mg/m^2 IV daily x 5 days q28d or chlorambucil 0.4 mg/kg PO once q14d (to max. 0.8 mg/kg as tolerated)
Catovsky: Fludarabine 25 mg/m^2 IV (or 40 mg/m^2 PO) daily x 5 days q28d or chlorambucil 10 mg/m^2 daily x 7 days q28d

Catovsky D, et al. Lancet 2007;370:230-39. Eichhorst BF, et al. Blood 2009;114:3382-91.

First-Line Treatment: Chlorambucil versus Fludarabine

- Fludarabine has shown improvement in PFS compared to chlorambucil, but this has not been demonstrated in all studies
- No differences exist in overall survival between the two; trend toward worse survival with fludarabine in one study
- Chlorambucil remains a good option for elderly patients or those unlikely to tolerate a purine analog

First-Line Treatment: Cladribine

- Randomized 229 subjects
  - Cladribine 0.12 mg/kg/day IV over 2 hours and prednisone 30 mg/m^2/day x 5 days OR
  - Chlorambucil 12 mg/m^2/day PO and prednisone 30 mg/m^2/day x 7 days
- Responses significantly better with cladribine plus prednisone
  - ORR 87% vs. 57% (p=0.001)
  - CR 47% vs. 12% (p=0.001)
  - PFS better with cladribine; no difference OS

Robak T, et al. Blood 2000;96:2723-9. Robak T, et al. Cancer 2009;115:94-100.
Karlsson KA, et al. Blood 2007;110:Abstract 194.

First-Line Treatment: Rituximab

Study	Dose and Schedule	Comments
O'Brien 2001 (n=50)	Dose 1: 375 mg/m^2 Dose 2+: range 500-2250 mg/m^2	Most toxicity occurred with first infusion (grade 1 and 2); 12% with hypoxia, dyspnea, hypotension; PR 36% (CLL); response increased with dose

O'Brien SM, et al. J Clin Oncol 2001;19(8):2165-70.

First-Line Treatment: Rituximab

Study	Dose and Schedule	Comments
Hainsworth 2003 n=44	375 mg/m^2 weekly x 4; If response or stable disease, repeat course every 6 months for total of 4 courses	ORR 58% (CR 9%) 1st course; PFS 18.6 months (20 month follow-up); PFS 1-year 62%; PFS 2-years 49%
Del Poeta 2008 n=75	Treated with fludarabine x 6 cycles, then rituximab 375 mg/m^2 x 4 weekly doses; if MRD+ (28 patients) monthly rituximab 375 mg/m^2 x 4 months, then 150 mg/m^2 x 12 months	Initial therapy (fludarabine plus rituximab x 4 doses) CR 81% and PR 13%; longer response duration in 28 patients with MRD given rituximab (87% vs. 32% at 5 years; p=0.001) versus no consolidation

Hainsworth JD, et al. J Clin Oncol 2003;21:1746-51. Del Poeta G, et al. Cancer 2008;112:119-28.

First-Line Treatment: Chlorambucil versus Alemtuzumab

CAM307 Study

	Alemtuzumab n=149	Chlorambucil n=148	p value
PFS	14.6 months	11.7 months	0.0001
ORR	83%	55%	<0.0001
CR	24%	2%	<0.0001
OS	84%	84%	NS

Median follow-up 24.6 months
Alemtuzumab 30 mg IV 3x/week up to 12 weeks
Chlorambucil 40 mg/m^2 every 28 days up to 12 months

Hillmen P, et al. J Clin Oncol 2007;25(35):5616-23.

First-Line Treatment: Consolidation with Alemtuzumab

- Several studies have addressed the role of alemtuzumab for consolidation following remission induction
  - German CLL Study Group
    - PFS significantly prolonged in patients randomized to alemtuzumab following treatment with fludarabine +/- cyclophosphamide
  - CALGB 10101
    - Alemtuzumab given following fludarabine plus rituximab
      - With 36 month follow-up, PFS was 36 months, 2-yr PFS 72%, 2-yr OS 86%
  - Severe infectious toxicity occurred in both studies

Lin TS, et al. J Clin Oncol 2010;28:4500-6. Schweighofer CD, et al. Br J Haematol 2009;144:95-8.

First-Line Treatment: Alemtuzumab

- Not recommended for routine consolidation due to infectious toxicity
- Reasonable single-agent option in patients unlikely to tolerate aggressive alkylator-based regimens
- Not highly effective in patients with bulky disease
- Efficacy demonstrated in patients with del(17p) because its mechanism is not dependent on p53
- Commonly administered subcutaneously rather than intravenously
- Prophylaxis recommended against HSV and *Pneumocystis; m*onitor for CMV reactivation and consider valganciclovir prophylaxis

First-Line Treatment: Chlorambucil versus Bendamustine

- Phase III randomized study comparing chlorambucil and bendamustine in 319 patients with previously untreated advanced CLL
  - Bendamustine 100 mg/m^2 IV daily on Days 1 and 2
  - Chlorambucil 0.8 mg/kg orally on Days 1 and 15
  - Repeated every 28 days for maximum 6 cycles

Knauf WU, et al. J Clin Oncol 2009;27:4378-84.

First-Line Treatment: Chlorambucil versus Bendamustine

	Bendamustine (n=162)	Chlorambucil (n=157)	p value
ORR	68%	31%	<0.0001
CR	31%	2%	<0.0001
PFS (ITT)	21.2 months	8.8 months	<0.0001
Gr 3/4 heme toxicity	40%	19%	-

No difference overall survival; patients achieving CR had longer OS than patients not in CR (median not reached vs. 76.2 months; p=0.002); QOL same in both treatment groups

Knauf WU, et al. J Clin Oncol 2009;27:4378-84. Knauf WU, et al. Blood 2010;116:Abstract 2449.

First-Line Treatment: Bendamustine and Rituximab

- German CLL Study Group
  - 117 patients with previously untreated CLL
- Treatment regimen (28-day cycles)
  - Bendamustine 90 mg/m^2 IV daily x 2 days
  - Rituximab 375 mg/m^2 IV once Cycle 1, then 500 mg/m^2 IV once Cycles 2-6
- Median follow-up 15.4 months
- ORR 90.9%
- CR 32.7%
- Median PFS not reached

Fischer K, et al. Blood 2009;114:Abstract 205.

First-Line Treatment: Combinations with Purine Analogs

- Several studies demonstrated benefit of combination therapy with fludarabine
  - Fludarabine plus cyclophosphamide versus fludarabine alone
  - Fludarabine plus concurrent rituximab versus fludarabine plus sequential rituximab
  - Fludarabine, cyclophosphamide, plus rituximab

Flinn IW, et al. J Clin Oncol 2007:25(7):793-8. Grever MR, et al. J Clin Oncol 2007;25(7):799-804. Eichhorst BF, et al. Blood 2006;107(3):885-91. Catovsky D, et al. Lancet 2007;370:230-9.
Byrd JC, et al. Blood 2003;101:6-14. Byrd JC, et al. Blood 2005;105:49-53.
Keating MJ, et al. J Clin Oncol 2005:23:4079-88. Tam CS, et al. Blood 2008:112:975-80.

First-Line Treatment: Fludarabine, Cyclophosphamide, and Rituximab

FCR Regimen			
Fludarabine	25 mg/m^2	daily x 3 days	Days 1-3
Cyclophosphamide	250 mg/m^2	daily x 3 days	Days 1-3
Rituximab	375 mg/m^2	once	Cycle 1, Day 0
	500 mg/m^2	once	Cycles 2-6, Day 1

Repeated cycles every 28 days for 6 cycles ; treatment discontinued after 3 cycles if no PR or CR

Hallek M, et al. Lancet 2010;376;1164-74.

First-Line Treatment: Fludarabine, Cyclophosphamide, and Rituximab

- German CLL Study Group (CLL8)
  - 817 patients with advanced, symptomatic CLL randomized to FCR or fludarabine and cyclophosphamide (FC)
- Primary endpoint progression-free survival
- Median age 61 years (30-81); 30% >= 65 years); relatively physically fit
- No prophylaxis with CSFs or antivirals; PCP prophylaxis if neutropenic > 7 days

Hallek M, et al. Lancet 2010;376;1164-74.

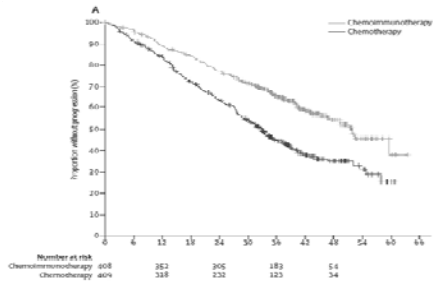
First-Line Treatment: Fludarabine, Cyclophosphamide, and Rituximab

			FC (%)	FCR (%)	p value
All	n=817	CR	22	44	<0.0001
		ORR	80	90	<0.0001
Del(17p)	n=51	CR	0	5	0.43
		ORR	34	68	0.025
Del(11q)	n=142	CR	15	51	<0.0001
		ORR	87	93	0.40
IgV$_H$ unmutated	n=390	CR	19	40	<0.0001
		ORR	76	91	<0.0001

Hallek M, et al. Lancet 2010;376;1164-74.

First-Line Treatment: Fludarabine, Cyclophosphamide, and Rituximab

Progression-Free Survival in All Patients



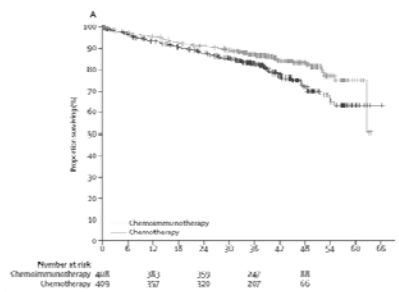
Median PFS
FCR 51.8 mo.
FC 32.8 mo.
P<0.0001

PFS at 3 yrs.
FCR 65%
FC 45%
P<0.0001

Reprinted with permission from Elsevier. Hallek M, et al. Lancet 2010;376;1164-74.

First-Line Treatment: Fludarabine, Cyclophosphamide, and Rituximab

Overall Survival

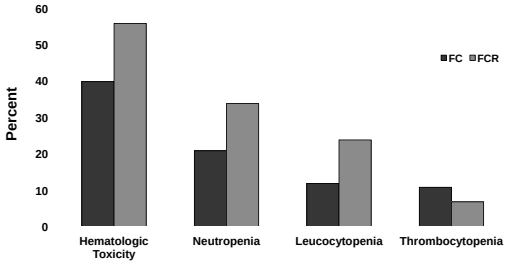


3 yr. OS
FCR 87%
FC 83%
P=0.012

Reprinted with permission from Elsevier. Hallek M, et al. Lancet 2010;376;1164-74.

First-Line Treatment: Fludarabine, Cyclophosphamide, and Rituximab

Incidence of Grade 3 and 4 Adverse Events



Reprinted with permission from Elsevier. Hallek M, et al. Lancet 2010;376;1164-74.

First-Line Treatment: FCR versus BR

- FCR strongly encouraged in guidelines for younger patients without co-morbidities
- Current trial ongoing to compare FCR to BR in first-line setting
  - German CLL 10 Protocol
  - Non-inferiority design

First-Line Treatment: Pentostatin, Cyclophosphamide, and Rituximab

- Pentostatin 2 mg/m^2 Day 1
- Cyclophosphamide 600 mg/m^2 Day 1
- Rituximab 375 mg/m^2 Day 1
  - First cycle 100 mg/m^2 Day 1, 375 mg/m^2 Day 3, and 375 mg/m^2 Day 5
- 65 patients
  - ORR 91%
    - CR 41%
    - Nodular PR 22%
    - PR 28%

Kay NE, et al. Blood 2007:109(2):405-11.

First-Line Treatment: HDMP and Rituximab

- High-dose methylprednisolone (HDMP)
  - 1 g/m^2 IV daily x 3 days with rituximab
  - Repeated every 28 days x 3 cycles
- 28 patients
  - ORR 96%
  - CR 32%
  - Median follow-up 3 years
    - PFS 30.3 months
- Option in patients with limited myeloid reserve, those with del(17p), immune cytopenias

Castro JE, et al. Leukemia 2009;23(10):1779-89.

Selection of First-Line Regimen

- Patient factors
  - Age
  - Co-morbidities
- Disease factors
  - Presence of poor prognostic factors
    - Del(17p)
      - – Chemotherapy or chemoimmunotherapy recommended in younger patients
      - – Older patients may respond well to alemtuzumab
    - Del(11q)
      - – Alkylator-based therapy recommended

Summary Slide First Line Therapy

Frail patient or co-morbidities	Age >=70 or younger with co-morbidities	Age < 70 or older with no co-morbidities
Chlorambucil +/- Pred	Chlorambucil +/- Pred	FCR
Rituximab	BR	FR
Corticosteroids	Cyclophosphamide, Pred +/- R	PCR
	Alemtuzumab	BR
	Rituximab	
	F +/- R	
	Cladribine	

B=bendamustine; R=rituximab; F=fludarabine; C=cyclophosphamide; P=pentostatin

NCCN. Non-Hodgkin's Lymphomas. v.1.2011. Available at: www.nccn.org/professionals/physician_gls/PDF/nhl.pdf

Summary Slide First Line Therapy

del(17p)	del(11q) and age >=70 or younger with co-morbidities	del(11q) and age < 70 or older with no co-morbidities
FCR	Chlorambucil +/- Pred	FCR
FR	BR	BR
HDMP + R	Cyclophosphamide, Pred +/- R	PCR
Alemtuzumab +/- R	Reduced-dose FCR	
BR	Alemtuzumab	
	Rituximab	

F=fludarabine; C=cyclophosphamide; R=rituximab; HDMP=high-dose methylprednisolone; B=bendamustine; P=pentostatin

NCCN. Non-Hodgkin's Lymphomas. v.1.2011. Available at: www.nccn.org/professionals/physician_gls/PDF/nhl.pdf

Treatment of Relapsed or Refractory CLL

Audience Response Question

3. At your institution, what is the preferred regimen for patients less than 70 years of age with standard-risk relapsed CLL?
   A. Fludarabine, cyclophosphamide, rituximab
   B. Bendamustine, rituximab
   C. Alemtuzumab
   D. Rituximab
   E. Ofatumumab
   F. Other

Relapsed/Refractory CLL: FCR

Previously-treated CLL
- Binet stage A 10%
- Binet stage B 59%
- Binet stage C 31%

Primary endpoint
- PFS

Stratification
- Prior therapy
  - Alkylator-refractory
  - Alkylator-sensitive
  - Fludarabine exposed
- Time from diagnosis

RANDOMIZE 1:1

Fludarabine Cyclophosphamide Rituximab (FCR) n=276

Fludarabine Cyclophosphamide (FC) n=276

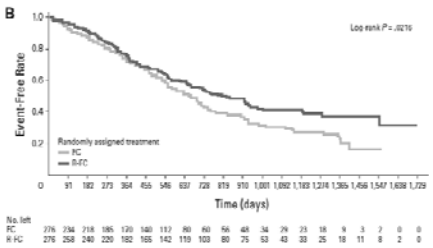
Robak T, et al. J Clin Oncol 2010;28:1756-65.

Relapsed/Refractory CLL: FCR REACH Study

- One prior line of therapy
  - Not alkylator or purine combination
  - If prior fludarabine, NOT refractory (response < 6 months); few had prior fludarabine exposure)
  - No prior rituximab
- Tumor lysis syndrome prophylaxis
- PCP and HSV prophylaxis
- CSFs allowed

Relapsed/Refractory CLL: FCR

Progression-Free Survival by Independent Review Panel

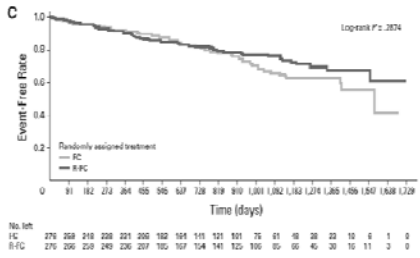


Median PFS
FCR 27 months
FC 21.9 months
P=0.0218
(median f/u 25 months)

Reprinted with permission from the American Society of Clinical Oncology. Robak T, et al. J Clin Oncol 2010;28:1756-65.

Relapsed/Refractory CLL: FCR

Overall Survival



Reprinted with permission from the American Society of Clinical Oncology. Robak T, et al. J Clin Oncol 2010;28:1756-65.

Relapsed/Refractory CLL: Bendamustine and Rituximab

- 81 patients (62 evaluable for response)
- Median number of 2 prior regimens
- Treatment
  - Bendamustine 70 mg/m^2 Days 1 and 2
  - Rituximab 375 mg/m^2 Day 1, Cycle 1
  - Rituximab 500 mg/m^2 Day 1, Cycles 2-6
  - Repeated every 28 days up to 6 cycles
- ORR 77.4%
- CR 14.5%
- PR 62.9%

Fischer K, et al. Blood 2008;112:Abstract 330.

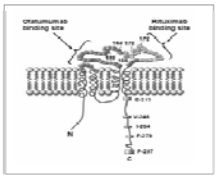
Relapsed/Refractory CLL: Alemtuzumab

- Several phase II studies have demonstrated efficacy of single agent alemtuzumab in the salvage setting
  - Fludarabine-refractory patients
    - ORR 33%; CR 2% (IV alemtuzumab)
    - ORR 34%; CR 4% (SC alemtuzumab)
  - Patients with p53 mutations or del(17p)
    - ORR 39-50%
- Current studies in combination with rituximab or fludarabine

Keating MJ, et al. Leuk Lymph 2002;43(9):1755-62. Stilgenbauer S, e al. J Clin Oncol 2009;27(24):3994-4001. Lozanski G, et al. Blood 2004;103:3278-81. Osuji NC, et al. Haematologica 2005;90(10):1435-6. Keating MJ, et al. Blood 2002;99:3554-61. Faderl S, et al. Blood 2003;101(9):3413-5. Stilgenbauer s. et al. N Engl J Med 2002;347(6):452-3. Karlsson C, et al. Br J Haematol 2009;144:78-85. Elter T, et al. J Clin Oncol 2005;23:7024-31.

Ofatumumab

- Anti-CD20 monoclonal antibody
- Binds to a different epitope of CD20 than rituximab
- Improved complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity compared to rituximab
- Approved for the treatment of CLL resistant to both fludarabine and alemtuzumab



Reprinted with permission from the American Society of Clinical Oncology. Cheson BD. J Clin Oncol 2010;25:3525-30.

Relapsed/Refractory CLL: Ofatumumab

- 206 patients with fludarabine- and alemtuzumab-refractory CLL (final analysis)
- Eight weekly doses of ofatumumab followed by 4 monthly doses
  - 300 mg x 1 dose, then 2000 mg x 11 doses
    - 89% completed 8 infusions
    - 50% completed 12 infusions
- Response evaluated over 24-week period

Wierda WG, et al. J Clin Oncol 2010;28:1749-55. Wierda WG, et al. Blood 2010;116(21): Abstract 921.

Relapsed/Refractory CLL: Ofatumumab

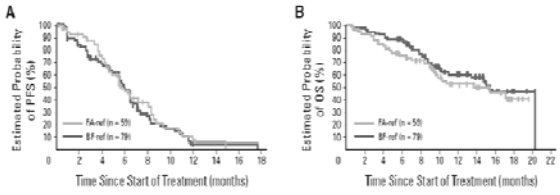
	FA-Ref	BF-Ref
Number of prior therapies	5 (1-14)	4 (1-16)
Rai Stage III-IV at screening (%)	61	70
Prior rituximab-containing regimen (%)	59	55
Overall response rate (ORR) (%)	51	44
Complete response (CR) (%)	0	2
Partial response (PR) (%)	51	42
Median response duration (months)	5.7	6
Median PFS (months)	5.5	5.5
Median overall survival (months)	14.2	17.4

FA-Ref (fludarabine- and alemtuzumab-refractory); BF-Ref (fludarabine-refractory with bulky (> 5 cm) lymphadenopathy); PFS (progression-free survival)

Wierda WG, et al. J Clin Oncol 2010;28:1749-55. Wierda WG, et al. Blood 2010;116(21): Abstract 921.

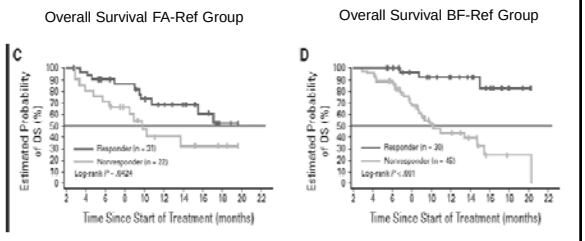
Relapsed/Refractory CLL: Ofatumumab

Progression-Free Survival and Overall Survival



Reprinted with permission from the American Society of Clinical Oncology. Wierda WG, et al. J Clin Oncol 2010;28:1749-55.

Relapsed/Refractory CLL: Ofatumumab



Reprinted with permission from the American Society of Clinical Oncology. Wierda WG, et al. J Clin Oncol 2010;28:1749-55.

Relapsed/Refractory CLL: Rituximab

Study	Dose and Schedule	Comments
Byrd 2001 (n=33)	Day 1: 100 mg Day 3: 250 mg/m^2 or 375 mg/m^2, then 3x/week x 4 weeks	ORR 45%

Byrd JC, et al. J Clin Oncol 2001;19(8):2153-64.

Relapsed/Refractory CLL: HDMP and Rituximab

- Regimen
  - Methylprednisolone 1 g/m2 IV daily x 5 days
  - Rituximab 375 mg/m2 IV weekly x 4 weeks
- Twenty-seven patients (Bowen)
  - Nine with del(17p) and six with del(11q)
  - ORR 78%; CR 22% after one cycle
  - Infectious complications 29% during first cycle
  - 3-year survival 41%
- Fourteen fludarabine-refractory patients (Castro)
  - ZAP-70 positive 79%
  - ORR 93%; CR 36% after 3 cycles
  - Median time to progression 15 months

Bowen DA, et al. Leuk Lymph 2007;48:2412-7. Castro JE, et al. Leukemia 2008;22:2048-53.

Selection of Regimens in Patients with Relapsed/Refractory CLL

- Patient factors
  - Age
  - Co-morbidities
- Disease factors
  - Duration of prior remission
  - Presence of poor prognostic factors
  - Repeat FISH before each subsequent therapy to further guide treatment
    - New cytogenetic abnormalities often acquired as disease progresses

Summary Slide Relapsed/Refractory Treatment

Frail patient or co-morbidities (without del(11q) or del(17p))	Age >=70 & short response (without del(17p))	Age < 70 or older with no co-morbidities & short response (without del(17p))
Chlorambucil +/- Pred	Reduced-dose FCR	FCR
Rituximab	Reduced-dose PCR	PCR
Corticosteroids	B +/- R	BR
	HDMP + R	Fludarabine + alemtuzumab
	Chlorambucil +/- Pred	CHOP-R
	Ofatumumab	HyperCVAD-R
	Alemtuzumab +/- R	Dose-adjusted EPOCH-R
	Dose-dense rituximab	OFAR
		Ofatumumab
		Alemtuzumab +/- R
		HDMP + R

F=fludarabine; C=cyclophosphamide; R=rituximab; P=pentostatin; B=bendamustine; HDMP=high-dose methylprednisolone; CHOP= cyclophosphamide, doxorubicin, vincristine, prednisone; HyperCVAD=cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high-dose methotrexate and cytarabine; EPOCH=etoposide, prednisone, vincristine, doxorubicin, cyclophosphamide; OFAR=oxaliplatin, fludarabine, cytarabine, rituximab; Short response= < 2 years; Long response = > 3 years
NCCN. Non-Hodgkin's Lymphomas. v.1.2011. Available at: www.nccn.org/professionals/physician_gls/PDF/nhl.pdf

Summary Slide Relapsed/Refractory Treatment

del(17p)
CHOP-R
CFAR
HyperCVAD-R
OFAR
Ofatumumab
Alemtuzumab +/- rituximab
High-dose dexamethasone +/- rituximab
Bendamustine +/- rituximab

CHOP= cyclophosphamide, doxorubicin, vincristine, prednisone; R=rituximab; CFAR=cyclophosphamide, fludarabine, alemtuzumab, rituximab; HyperCVAD=cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high-dose methotrexate and cytarabine; OFAR=oxaliplatin, fludarabine, cytarabine, rituximab
NCCN. Non-Hodgkin's Lymphomas. v.1.2011. Available at: www.nccn.org/professionals/physician_gls/PDF/nhl.pdf

Hematopoietic Stem Cell Transplantation

Audience Response Question

4. For patients in whom hematopoietic stem cell transplantation (HSCT) is indicated, which of the following is preferred?
   A. Autologous HSCT
   B. Ablative allogeneic HSCT
   C. Nonmyeloablative allogeneic HSCT
   D. Donor lymphocyte infusion

Autologous and Allogeneic Stem Cell Transplantation

- Retrospective analysis of 162 patients with CLL at Dana Farber (1989-99)
- Matched sibling allogeneic HSCT (n=25) and autologous HSCT (n=137)
- Ablative conditioning with total body irradiation and cyclophosphamide
- No difference in overall survival with median follow-up of 6.5 years
- High rate of treatment-related complications
- Low relapse rate in allogeneic group at 2 years with evidence of graft-versus-leukemia

Gribben JG, et al. Blood 2005;106:4389-96.

Allogeneic Stem Cell Transplant

- Retrospective evaluation of the Center for International Blood and Marrow Transplant Research
- 38 CLL patients underwent myeloablative conditioning followed by matched unrelated donor transplant
  - Chemotherapy-refractory 55%; prior fludarabine in 89%
  - CR 58%; PR 17%
  - Grade 2-4 acute GVHD 45%; chronic 85% at 5 years
  - 5-year OS 33%; treatment-related mortality 38%

Pavletic SZ, et al. J Clin Oncol 2005;23:5788-94.

Allogeneic Stem Cell Transplant

- Reduced intensity (German CLL3X) conditioning with fludarabine- and cyclophosphamide-based regimen (n=90)
- Median follow-up 46 months
  - 4-year non-relapse mortality 23%
  - 4-year event-free survival 42%
  - Overall survival 65%
  - 27 (52%) of 52 patients with monitoring available for minimal residual disease (MRD) were alive and MRD negative at 12 months
  - Uncontrolled disease at transplant and T-cell depletion with alemtuzumab were poor prognostic factors

Dreger P, et al. Blood 2010;116(14):2438-47.

Allogeneic Stem Cell Transplant

- 50 patients (1996-2006)
  - 21 reduced-intensity conditioning (RIC)
  - 29 full-intensity conditioning (FIC)
- 5-year OS
  - RIC 63% versus FIC 18% (p=0.006)
- Transplant-related mortality at Day 100
  - RIC 14% versus FIC 27% (p=0.005)
- Relapse rate 15%

Peres E, et al. Bone Marrow Transplant 2009;44:579-83.

Allogeneic Stem Cell Transplant: Reduced Intensity Conditioning

- 82 patients with fludarabine-refractory CLL
  - Conditioning regimen 2 Gy total-body irradiation (TBI) +/- fludarabine
  - Related (n=52) or unrelated donors (n=30)
- CR 55% and PR 15%
- 5-year incidence
  - Non-relapse mortality 23%
  - Progression/relapse 38%
  - Overall survival 50%
  - PFS 39%

Sorror ML, et al. J Clin Oncol 2008;26:4912-4920.

Allogeneic Stem Cell Transplant: Reduced Intensity Conditioning

- European Group for Blood and Marrow Transplantation (EBMT) reported on 44 patients with del(17p)
  - Matched related donor (n=24) or matched unrelated donor (n=20)
  - 5 myeloablative; 39 reduced intensity
  - 53% in remission at HSCT
  - 3-year OS 44%; PFS 37%
  - Grade 2-4 acute GVHD 43%; extensive chronic GVHD 53%
  - No late relapses in 9 patients after 4+ years

Schetelig J, et al. J Clin Oncol 2008;26:5094-100.

Indications for Allogeneic HSCT: NCCN Guidelines

- Without del(11q) or del(17p)
  - Consider after short response to salvage therapy
- With del(17p)
  - Consider if achieve CR or PR to first-line therapy
- With del(11q)
  - Consider if achieve PR to first-line therapy
  - If CR, observe and retreat with non-transplant modality at disease progression

NCCN. Non-Hodgkin's Lymphomas. v.1.2011. Available at: www.nccn.org/professionals/physician_gls/PDF/nhl.pdf

Indications for Allogeneic HSCT: EBMT Transplant Consensus

- Option for younger patients with one of the following poor-risk features:
  - Non-response or early relapsed (within 12 months) after purine analogs
  - Relapse within 24 months after response with purine-analog-based combination therapy or autologous transplantation
  - Patients with p53 abnormalities (del(17p)) requiring treatment

Dreger P, et al. Leukemia 2007;21:12-7.

Conclusions

- FCR has become the standard for first-line treatment of CLL in patients able to tolerate this therapy
- FCR is the treatment of choice for most patients in the second-line setting
- It is not clear which regimen patients should receive for salvage if they receive FCR in the first-line setting
- Many other treatment options are available for patients unable to tolerate highly intensive regimens
- Greater support is now available for reduced-intensity allogeneic stem cell transplantation in selected patients with CLL that have a suitable donor

BCOP RECERTIFICATION

Chronic Lymphocytic Leukemia: Treatment Update

Ashley Morris Engemann, PharmD, BCOP
Clinical Associate
Duke University Medical Center
March 2011

BCOP RECERTIFICATION

Updates in the Treatment of Metastatic Breast Cancer

Michael J. Berger, Pharm.D., BCOP
Specialty Practice Pharmacist,
The James Comprehensive Breast Center,
The James Cancer Hospital and Solove Research Institute at
The Ohio State University

Faculty Disclosure

- Michael Berger has no areas of conflict to disclose.

Objectives

- Discern the role of bevacizumab in the management of patients with metastatic breast cancer (MBC)
- Compare and contrast targeted therapies for the treatment of HER2$^{(+)}$ MBC
- Distinguish chemotherapy treatment options for patients with anthracycline and taxane-refractory MBC based on efficacy and tolerability
- Appraise emerging, novel treatment strategies to determine the value of further study and anticipated toxicity profile

MBC - Background

- 5-10% breast cancer patients initially present with MBC
- Heterogeneous behavior
- Median survival ≈ 3 years
- Goals of therapy
  - Palliation, quality of life, prolong survival
- < 5% patients live 5 years
  - Curable subset?

Pagani O et al. JNCI. 2010; 102(7):1-8

MBC - Background

- Factors which influence treatment initiation and continuation:
  - Estrogen / Progesterone receptor (ER/PR) status
  - HER2 status
  - Duration of relapse-free interval
  - Location and extent of metastases
  - Previous treatment
  - Patient symptoms, performance status
- Sequential single agent vs. combination

Beslija S et al. Ann of Oncol. 2009;20:1771-1785

Objectives

- **Discern the role of bevacizumab in the management of patients with metastatic breast cancer (MBC)**
- Compare and contrast targeted therapies for the treatment of HER2$^{(+)}$ MBC
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- Appraise emerging, novel treatment strategies to determine the value of further study and anticipated toxicity profile

Phase III Trial of Paclitaxel ± Bevacizumab in First-line MBC (E2100)

MBC
- Previously untreated locally recurrent or MBC, HER2(–)

Primary endpoint
- PFS in months (mo) by independent review facility (IRF)

Stratification
- Disease-free interval
- Adjuvant therapy
- ER+, ER–, unknown
- Number of metastatic sites

RANDOMIZE 1:1

Paclitaxel 90 mg/m² days 1, 8, 15 q 28 days (n=326)

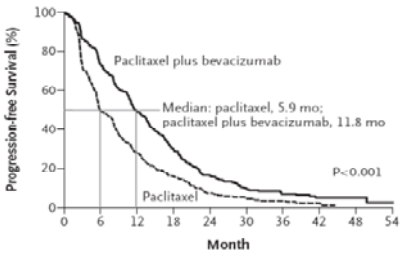
Treat until disease progression, no crossover permitted

Paclitaxel 90 mg/m² days 1, 8, 15 q 28 days + Bevacizumab 10 mg/kg days 1, 15 q 28 days (n=347)

Miller KD et al. NEJM. 2007; 357(26):2666-76

Phase III Trial of Paclitaxel ± Bevacizumab in First-line MBC (E2100)

Kaplan-Meier estimate of PFS:



Reprinted with permission from the *NEJM*.
Miller KD et al. NEJM. 2007; 357(26):2666-76

No significant difference in OS

Chemotherapy ± Bevacizumab in First-line MBC: Study Designs

	E2100[1]	AVADO[2]	RIBBON-1[3]
Placebo (Pl) Controlled	No	Yes	Yes
Chemotherapy	Paclitaxel (P)	Docetaxel (D)	Capecitabine (C), Taxanes (T) Anthracyclines (A)
Bevacizumab (B)	10 mg/kg Q2 weeks	15 mg/kg Q3 weeks	15 mg/kg Q3 weeks
Primary Endpoint	PFS	PFS	PFS

1. Miller KD et al. NEJM. 2007; 357(26):2666-76 2. Miles DW, et al. J Clin Oncol. 2010; 28(20):3239-47
3. Roberts NJ et al. Proc Am Soc Clin Oncol. 2009; Abstract 1005

Chemotherapy ± Bevacizumab in First-line MBC: Efficacy

	E2100[1]		AVADO[2]		RIBBON-1[3]			
Chemo	P	P + B	D + Pl	D + B	C + Pl	C + B	A or T + Pl	A or T + B
PFS, mo	5.9	11.8	8.2	10.1	5.7	8.6	8.0	9.2
HR	0.60 p < 0.001		0.77 p = 0.006		0.69 p = 0.0002		0.64 p < 0.0001	
OS, mo	25.2	26.7	31.9	30.2	21.2	29	23.8	25.2

1. Miller KD et al. NEJM. 2007; 357(26):2666-76 2. Miles DW, et al. J Clin Oncol. 2010; 28(20):3239-47
3. Roberts NJ et al. Proc Am Soc Clin Oncol. 2009; Abstract 1005

Chemotherapy ± Bevacizumab in First-line MBC: Safety

Selected grade ≥ 3 Adverse Events (AEs), %	Chemotherapy + Bevacizumab (n = 1679)	Chemotherapy (n = 982)
Neutropenia	10	7.1
Sensory neuropathy	9.5	8.5
Hypertension	9	1.2
Febrile Neutropenia	6.5	3.5
Proteinuria	2.3	0
Thrombotic event	2.8	3.8
Treatment related death	2.1	1.8

O'Shaughnessy J et al. Proc Am Soc Clin Oncol. 2010; Abstract 1005

Bevacizumab – Audience Response Question

Which of the following statements regarding the use of bevacizumab in the treatment of MBC is most accurate and compelling?

1. Significant PFS advantage in combination with 2nd line chemotherapy
2. Significant OS advantage in combination with 1st line chemotherapy
3. Significant ORR advantage in combination with capecitabine 1st or 2nd line
4. Significant PFS advantage in combination with 1st line chemotherapy

Role of Bevacizumab in MBC - Summary

- Significant advantage in PFS (primary endpoint) when bevacizumab added to chemotherapy for 1st line MBC
  - Combination with weekly paclitaxel appears most efficacious
- No OS advantage
- No *new* safety concerns
- July 2010 – ODAC[1] ruling
- December 2010 – FDA[2] initiated process to withdraw prior accelerated approval
- FDA Label remains unchanged
- Future

[1]Oncologic Drugs Advisory Committee [2]Food and Drug Administration

Objectives

- Discern the role of bevacizumab in the management of patients with metastatic breast cancer (MBC)
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Chemotherapy ± Trastuzumab: First Line Treatment of HER2(+) MBC

Historical efficacy for 1st line treatment	Median TTP, mo	Median OS, mo
Paclitaxel or Doxorubicin + Cyclophosphamide (AC)[1]	4.6	20.3
Paclitaxel or AC + Trastuzumab[1]	**7.4** p < 0.001	**25.1** p = 0.046
Docetaxel[2]	6.1	22.7
Docetaxel + Trastuzumab[2]	**11.7** p = 0.0001	**31.2** p = 0.0325
Paclitaxel + Trastuzumab[3]	7.1	32.2
Paclitaxel + Carboplatin + Trastuzumab[3]	**10.7** p = 0.03	35.7
Vinorelbine + Trastuzumab[4]	15.3	38.8
Docetaxel + Trastuzumab[4]	12.4	35.7

1. Slamon DJ, et al. NEJM 2001;344(11):783-92 2. Marty M, et al. J Clin Oncol 2005; 23: 4265-74
3. Robert N et al. J Clin Oncol. 2006;24(18):2786-92 4. Andersson M, et al. J Clin Oncol. 2010 Dec 13. [Epub ahead of print]

Chemotherapy ± Trastuzumab: Second Line Treatment of HER2(+) MBC - "Trastuzumab Beyond Progression Trial"

MBC
- HER2(+), progressive, locally advanced breast cancer (LABC) or MBC
- Previous trastuzumab
- Trastuzumab-free interval < 6 weeks
- Left ventricular ejection fraction (LVEF) ≥ 50%

Primary endpoint
- TTP

Stratification
- Previous treatment
- Participating center

RANDOMIZE 1:1

Trastuzumab
6 mg/kg q 21 days
+
Capecitabine 1250 mg/m²
BID × 14 days
q 21 days (n=78)

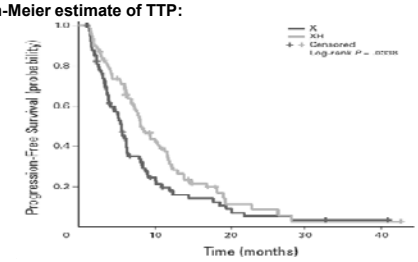
Treat until unacceptable toxicity or disease progression

Capecitabine 1250 mg/m²
BID × 14 days
q 21 days (n=78)

Von Minckwitz et al. J Clin Oncol. 2009; 27(12):1999-2006

Chemotherapy ± Trastuzumab: Second Line Treatment of HER2(+) MBC - "Trastuzumab Beyond Progression Trial"

Kaplan-Meier estimate of TTP:



Significant difference in TTP: 8.2 vs 5.6 mo
No significant difference in OS

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Von Minckwitz et al. J Clin Oncol. 2009; 27(12):1999-2006

Chemotherapy ± Lapatinib: Second Line Treatment of HER2(+) MBC

MBC
- Progressive, HER2(+) LABC or MBC
- Previous treatment with anthracycline, taxane and trastuzumab
- Normal left ventricular ejection fraction (LVEF)

Primary endpoint
- TTP by IRF

Stratification
- Disease stage
- Presence or absence of visceral disease

RANDOMIZE 1:1

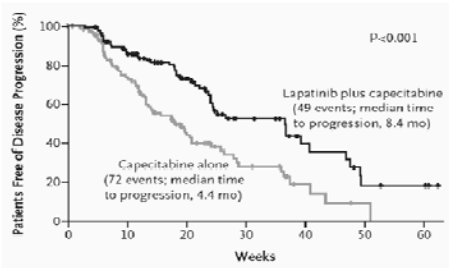
Lapatinib 1250 mg daily
+
Capecitabine 1250 mg/m²
BID × 14 days
q 21 days (n=163)

Capecitabine 1250 mg/m²
BID × 14 days
q 21 days (n=161)

Geyer et al. NEJM. 2006; 355(26):2733-43

Chemotherapy ± Lapatinib: Second Line Treatment of HER2(+) MBC

Kaplan-Meier estimate of TTP:



Reprinted with permission from the *NEJM*.
Geyer et al. NEJM. 2006; 355(26):2733-43

No significant difference in OS

Chemotherapy ± Lapatinib: Second Line Treatment of HER2(+) MBC

Selected any grade AEs, %	Capecitabine + Lapatinib	Capecitabine
Diarrhea	60	39
Stomatitis	15	12
Hand-foot syndrome	49	49
Rash	27	15
Fatigue	18	27
Dyspepsia	11	3
Cardiac events	2	0.7

Geyer et al. NEJM. 2006; 355(26):2733-43

Phase III Trial of Lapatinib ± Trastuzumab in HER2(+) MBC

MBC
- HER2(+) MBC
- Previous progression on trastuzumab
- Heavily pretreated, including anthracycline and taxane in adjuvant or metastatic setting

Primary endpoint
- PFS

Stratification
- Visceral disease
- Hormone receptor status

RANDOMIZE 1:1

Lapatinib 1500 mg daily (n = 148)

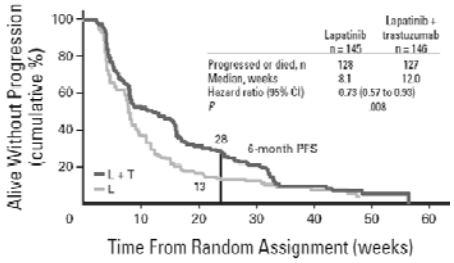
Optional crossover to trastuzumab arm if progressive disease after 4 wks (n = 77)

Trastuzumab
4 mg/kg loading dose then 2 mg/kg q 7 days
+
Lapatinib 1000 mg daily (n=148)

Blackwell K, et al. J Clin Oncol. 2010;28(7):1124-30

Phase III Trial of Lapatinib ± Trastuzumab in HER2(+) MBC

Kaplan-Meier estimate of PFS:



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Blackwell K, et al. J Clin Oncol. 2010;28(7):1124-30

No significant difference in OS

Targeted Therapy + Endocrine Therapy in Chemo Naive HER2(+) MBC

- Anastrozole vs. Anastrozole + Trastuzumab[1]
  - Postmenopausal, HER2(+), ER+, MBC
  - Primary endpoint – PFS
  - PFS - 5.6 mo (combination) vs. 3.8 mo anastrozole, HR 0.62, p = 0.006
- Letrozole vs. Letrozole + Lapatinib[2]
  - Postmenopausal, HER2(+), ER+, MBC
  - Primary endpoint: PFS in Her2(+) group
  - PFS – 8.2 mo (combination) vs. 3 mo letrozole, HR 0.71, p = 0.019

1. Kaufman B et al. J Clin Oncol. 2009;27(33):5529-37 2. Johnston et al. J Clin Oncol. 2009;27(33):5538-46

Lapatinib Monotherapy in HER2(+) CNS Disease

Crosses the blood brain barrier (BBB)
- Subset of capecitabine + lapatinib vs. capecitabine[1]
- Pilot study[2], n=39
  - Progressive brain metastases, prior trastuzumab, at least one measurable brain lesion
  - ORR 2.6%, median TTP 3 mo
- Phase II trial[3], n=242
  - Brain mets developed while on previous trastuzumab
  - Completed cranial radiation
  - ORR 6%, median PFS 2.4 mo

1. Geyer et al. NEJM. 2006; 355(26):2733-43 2. Lin NU et al. J Clin Oncol. 2008; 26(12):1993-9
3. Lin NU et al. Clin Cancer Res. 2009;15(4):1452-9.

Targeted Therapy – Audience Response Question

JW is an 65 yo female with HER2+ MBC to her bones and liver. She has received Docetaxel + Trastuzumab for over 6 months but restaging scans reveal progressive systemic disease as well as new lesions in her brain. Her ECOG is 0. Following radiation therapy, what chemotherapy is most appropriate for JW?

1. Gemcitabine + Cisplatin + Trastuzumab
2. Capecitabine + Trastuzumab
3. Capecitabine + Lapatinib
4. Trastuzumab + Lapatinib

"Targeted Therapy" Options for HER2(+) MBC - Summary

- Trastuzumab - significant ↑ PFS and OS in first line when combined with chemotherapy
- Trastuzumab - may continue post-progression, combine with different chemotherapy
- Lapatinib - significant ↑ in PFS in second line when combined with capecitabine in trastuzumab refractory patients
- Trastuzumab + Lapatinib - well tolerated, may be used in salvage setting for heavily pretreated patients
- Trastuzumab or Lapatinib - may be combined with endocrine therapy in the first line treatment of appropriately selected HER2+, ER+ patients

Objectives

- Discern the role of bevacizumab in the management of patients with metastatic breast cancer (MBC)
- Compare and contrast targeted therapies for the treatment of HER2(+) MBC
- **Distinguish chemotherapy treatment options for patients with anthracycline and taxane-refractory MBC based on efficacy and tolerability**
- Appraise emerging, novel treatment strategies to determine the value of further study and anticipated toxicity profile

Options for Anthracycline & Taxane Refractory MBC

- More patients exposed to both anthracyclines and taxanes in neo/adjuvant setting
- Definition for "resistant" or "refractory" disease as inclusion criteria in clinical trials may vary
  - Progressive disease during treatment
  - Recurrence within 6 months of neo/adjuvant therapy
  - Recurrence within 6-12 months of last dose in metastatic setting
  - Not defined

Gemcitabine Monotherapy Following Anthracyclines and Taxanes

Study	n	Phase	Median PFS, mo	Median OS, mo	ORR
Rha	38	II	**4.5**	11	20%
Smorenburg	23	II	**1.9 (TTP)**	7.8	0%
Modi	18	II	NR	9.5	17%
Suzuki	56	II	**3**	17.8	8.1%
Spielmann*	47	II	NR	NR	29%

*Prior therapy included only an anthracycline

Rha SY et al. Breast Cancer Res Treat. 2005;90:215-221.
Modi S et al. Clin Breast Cancer. 2005;6:55-60.
Smorenburg CH et al. Breast Cancer Res Treat. 2001;66(1):83-7
Suzuki Y et al. Jpn J Clin Oncol. 2009;39(11):699-706
Spielmann M et al. Oncology. 2001;60(4):303-7

Vinorelbine Monotherapy Following Anthracyclines and Taxanes

Study	n	Phase	Median PFS, mo	Median OS, mo	ORR
Zelek	40	II	**6 (TTP)**	6	25%
Livingston*	40	II	**3.3 (TTP)**	8.3	25%
Martin	126	III	**4**	16.4	26%
Degardin†	100	II	**3 (TTF)**	23.5	16%
Terzoli*†	80	II	**9 (TTP)**	19	52.5%

* Required GCSF support † Prior therapy included only an anthracycline

Zelek L et al. Cancer. 2001;92(9):2267-72.
Livingston RB et al. J Clin Oncol.1997;15(4):1395-400
Martin M et al. Lancet Oncol. 2007;8(3):219-25
Degardin M et al. Ann Oncol. 1994;5:423-426
Terzoli E et al. J Exp Clin Cancer Res. 2004;23:207-213

Capecitabine Monotherapy Following Anthracyclines and Taxanes

Study	n	Phase	Median PFS, mo	Median OS, mo	ORR
Blum	135	II	**3.1 (TTP)**	12.6	20%
Venturini	631	III	**6.6 (TTP)**	10	34.7%
Miller	230	III	**4.2**	14.5	9.1
Thomas	377	III	**4.2**	11.1	14%
Reichardt	136	II	**3.5 (TTP)**	10.1	15%
Fumoleau	126	II	**4.9 (TTP)**	15.2	28%

Blum JL et al. J Clin Oncol. 1999 Feb;17(2):485-93.
Venturini M et al. Oncology. 2007;72(1-2):51-7
Miller KD et al. J Clin Oncol. 2005;23:792-799.
Reichardt P et al. Ann Oncol. 2003;14:1227-1233.
Fumoleau P et al. Eur J Cancer. 2004;40:536-542.
Thomas ES et al. J Clin Oncol. 2007;25(33):5210-7

Phase III Trials of Capecitabine ± Ixabepilone in Patients Previously Treated With an Anthracycline and Taxane

	Anthracycline & Taxane "Resistant" [1]	Anthracycline & Taxane "Pretreated" [2]
Previous Chemo	**≤ 3 total**	**≤ 2 total**
Placebo Controlled	**No**	**No**
n	**752**	**1221**
Chemotherapy	**Capecitabine (C) 2000 mg/m² daily × 14 days ± Ixabepilone (I) 40 mg/m² Q3 weeks**	
Primary Endpoint	**PFS**	**OS**

1. Thomas ES et al. J Clin Oncol. 2007;25(33):5210-7 2. Sparano JA et al. J Clin Oncol. 2010;28(20):3256-63

Phase III Trials of Capecitabine ± Ixabepilone: Efficacy

	Anthracycline & Taxane "Resistant" [1,3]		Anthracycline & Taxane "Pretreated" [2]	
Chemo	**C**	**C + I**	**C**	**C + I**
PFS, mo	**4.2**	**5.8**	**4.4**	**6.2**
HR	**0.75, p = 0.0003**		**0.79, p = 0.005**	
OS, mo	**11.1**	**12.9**	**15.6**	**16.4**
HR	**0.9, p = 0.19**		**0.9, p = 0.1162**	
ORR	**14%**	**35%**	**29%**	**43%**

1. Thomas ES et al. J Clin Oncol. 2007;25(33):5210-7 2. Sparano JA et al. J Clin Oncol. 2010;28(20):3256-63
3. Hortobagyi GN et al. Breast Cancer Res Treat. 2010;122(2):409-18

Phase III Trial of Capecitabine ± Ixabepilone: Safety

Selected grade ≥ 3 AEs, %	Capecitabine + Ixabepilone	Capecitabine
Neutropenia	**68**	**11**
Peripheral sensory neuropathy	**23**	**0**
Hand-foot syndrome	**18**	**17**
Fatigue	**9**	**3**
Asthenia	**7**	**1**
Diarrhea	**6**	**8**
Febrile Neutropenia	**5**	**0.5**

Thomas ES et al. J Clin Oncol. 2007;25(33):5210-7

Phase II Trial of Ixabepilone in Anthracycline, Taxane and Capecitabine Refractory Patients

- MBC or LABC
- Resistance: disease progression while receiving therapy for MBC or recurrence within 6 months of neo/adjuvant
- n = 113
- Primary end point - ORR by IRF
  - ORR – 11.5%
- Secondary endpoint – PFS
  - 3.1 mo

Perez E et al. J Clin Oncol. 2007;25(23):3407-14

Eribulin Mesylate (Halaven™)

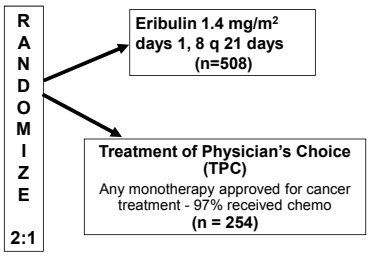
- Novel microtubule inhibitor
  - Prevents spindle formation
- Synthetic analogue of halichondrin B (sea sponge)
- Given as IV bolus (2-5 min), days 1 and 8 q 21 days
  - Incompatible with dextrose
  - Dose reduce in mild/moderate hepatic dysfunction
  - Dose reduce for CrCl < 50 mL/minute
- Negligible CYP3A4 activity
  - excreted unchanged in feces
  - no active metabolites

Phase III Trial of Eribulin vs Treatment of Physician's Choice (EMBRACE)

MBC
- Heavily pretreated (median 4 regimens), at least 2 for MBC
- Previous anthracycline and taxane-based chemo

Primary endpoint
- OS by IRF

Stratification
- Geographic region
- Previous capecitabine treatment
- HER2 status



Twelves C, et al. Proc Am Soc Clin Oncol 2010. Abstract CRA1004.

Phase III Trial of Eribulin vs TPC: Efficacy

	Eribulin	TPC
OS, mo	13.1	10.7
HR	0.81, p = 0.041	
PFS, mo	3.7	2.2
HR	0.85, p = 0.14	
ORR	12%	5%

Twelves C, et al. Proc Am Soc Clin Oncol 2010. Abstract CRA1004.

Phase III Trial of Eribulin vs TPC: Safety

Selected grade ≥ 3 AEs, %	Eribulin	TPC
Neutropenia	45	21.1
Febrile neutropenia	4.2	1.2
Asthenia / fatigue	8.8	10.1
Peripheral neuropathy	8.2	2
Dyspnea	3.6	2.8

Twelves C, et al. Proc Am Soc Clin Oncol 2010. Abstract CRA1004

Phase II Trial of Paclitaxel-albumin bound in Taxane Refractory MBC

- MBC - disease progression while receiving taxane-based treatment for MBC (or within 12 months of adjuvant treatment)
- > 50% of patients received adjuvant anthracyclines
- 100 mg/m^2 (n=106) or 125 mg/m^2 (n=75) given on days 1, 8, 15 q 28 days
- Primary endpoint – ORR
  - 14.1% and 16% respectively
- Secondary endpoint – PFS
  - 3 mo and 3.5 mo respectively

Blum JL et al. Clin Breast Cancer. 2007;7(11):850-6

Chemo for Anthracycline and Taxane Resistance - Audience Response Question

CD is a 54 yo female who received FEC x 4 cycles followed by weekly paclitaxel x 12 cycles as neoadjuvant treatment of her locally advanced, HER2$^{(-)}$ breast cancer. Six months after surgery and radiation, CD is diagnosed with metastatic disease in her chest wall. Which of the following monotherapy treatment options would be most appropriate for CD?

1. Capecitabine
2. Ixabepilone
3. Paclitaxel-albumin bound
4. Vinorelbine

Chemotherapy Options for Anthracycline and Taxane Refractory MBC - Summary

- Phase III data exists:
  - Capecitabine
  - Capecitabine + Ixabepilone
  - Vinorelbine
  - Eribulin
- Combination therapy may ↑ ORR and ↑ PFS
- Expected toxicity (cost?) influence treatment choice
- No head-to-head monotherapy comparisons
- Anthracycline, taxane and capecitabine refractory
  - Ixabepilone
  - Eribulin

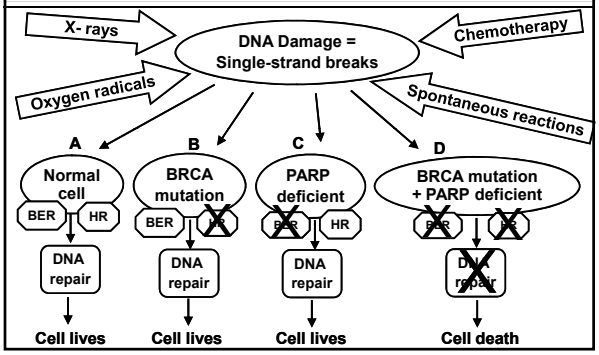
Objectives

- Discern the role of bevacizumab in the management of patients with metastatic breast cancer (MBC)
- Compare and contrast targeted therapies for the treatment of HER2$^{(+)}$ MBC
- Distinguish chemotherapy treatment options for patients with anthracycline and taxane-refractory MBC based on efficacy and tolerability
- **Appraise emerging, novel treatment strategies to determine the value of further study and anticipated toxicity profile**

"PARP" Inhibitors

- Key mechanisms of DNA repair:
  - BRCA1 / BRCA2 pathway
    - homologous recombination (HR) of double strands
  - PARP1 - poly (ADP-Ribose) polymerase 1
    - base excision repair (BER) of single strand breaks
- PARPs:
  - Large family of multifunctional enzymes
  - Most abundant is PARP1
- Characteristics of triple negative breast cancer (TNBC)
  - Shares common features of hereditary BRCA1
  - PARP1 up-regulated
- Analogy of table with 4 legs
- Agents: olaparib, veliparib, iniparib

Mechanisms of DNA Repair



Randomized Phase II Trial of Gem/Carbo ± Iniparib in Triple-Negative MBC

MBC
- ≤ 2 previous chemotherapies for MBC
- No prior gemcitabine, platinum agent, or PARP inhibitor

Primary endpoint
- Clinical benefit rate (CBR)

Stratification
- NR

RANDOMIZE 1:1

Iniparib 5.6 mg/kg IV, Days 1, 4, 8, 11
+ Gemcitabine 1000 mg/m²
+ Carboplatin AUC = 2,
Days 1, 8 q 21 days (n = 61)

Crossover to experimental arm allowed at progression

Gemcitabine 1000 mg/m² + Carboplatin AUC = 2,
Days 1, 8 q 21 days (n = 62)

1. O'Shaughnessy J, et al. N Engl J Med. 2011 Jan 20;364(3):205-14

Phase II Trial of Gem/Carbo ± Iniparib in Triple-Negative MBC: Efficacy

	Iniparib + Gem/Carbo	Gem/Carbo
CBR	56%	34%
p value	0.01	
OS, mo	12.3	7.7
HR	0.57, p = 0.01	
PFS, mo	5.9	3.6
HR	0.59, p = 0.01	

1. O'Shaughnessy J, et al. N Engl J Med. 2011 Jan 20;364(3):205-14

Phase II Trial of Gem/Carbo ± Iniparib in Triple-Negative MBC: Safety

Selected grade ≥ 3 AEs[1], %	Iniparib + Gem/Carbo	Gem/Carbo
Fatigue	7	19
Diarrhea	2	2
Vomiting	2	2
Nausea	0	2
Neutropenia	67	63
Anemia	23	15
Thrombocytopenia	37	27
Febrile neutropenia[2]	0	7

1. O'Shaughnessy J, et al. N Engl J Med. 2011 Jan 20;364(3):205-14
2. O'Shaughnessy J, et al. Proc San Antonio Breast Cancer Symposium. 2009. Abstract 3122

Trastuzumab-DM1 - "T-DM1"

- Trastuzumab linked to "DM1" – derivative of antimicrotubule inhibitor maytansanine
- Phase I[1], n = 24
  - Progressed on prior trastuzumab
  - 3.6 mg/kg IV q 21 days - MTD
  - Grade 4 thrombocytopenia - DLT
- Phase II[2], n = 112
  - Single arm, previous targeted therapy for MBC with disease progression (RECIST) within 60 days of last treatment
  - ORR – 25.9%, PFS – 4.6 mo
  - Grade 3 or worse AE: hypokalemia (8.9%), thrombocytopenia (8%), fatigue (4.5%)

[1] Krop IE et al. J Clin Oncol. 2010 Jun 1;28(16):2698-704.
[2] Burris HA 3rd et al. J Clin Oncol. 2010 Dec 20. [Epub ahead of print]

Emerging Therapies - Audience Response Question

MK is a 44 yo female with a PMH of triple negative breast cancer for which she received adjuvant anthracycline and taxane-based regimens. Following diagnosis of MBC, MK received capecitabine + bevacizumab for MBC. Her disease has now progressed. Which of the following treatment options has exhibited minimal toxicity and a possible survival advantage in the treatment of triple negative MBC?

1. Eribulin
2. Trastuzumab-DM1
3. Ixabepilone
4. PARP1 inhibitor + chemotherapy

Thank You

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