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Defining Aggressive Disease in Patients With Advanced NSCLC Receiving Second-Line Treatment: A Systematic Review

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BACKGROUND

- Recent randomized clinical trials (RCTs) have explored survival benefits of second-line treatments (2LTs) in patients who have rapidly progressed and/or are refractory to first-line treatment.
  - These trials have demonstrated an existing unmet need for patients with aggressive non-small cell lung cancer (NSCLC).
  - However, specific characterization of aggressive NSCLC is lacking, and there are many considerations for how best to define these patients.

OBJECTIVE

- The objective of this systematic literature review (SLR) was to explore the clinical trial definitions of aggressive NSCLC, and the number of studies reporting efficacy and safety outcomes by AD characteristic.

METHODS

- **Protocol:** The SLR was conducted using a predefined protocol in line with Cochrane methodology[1] and following Preferred Reporting Items for Systematic Reviews and Meta-Analyses[2] recommendations.
- **Search Strategy:** Medline, Embase, BioSciences Information Service, the Cochrane Library (to October 17, 2017), conference abstracts from scientific meetings (through October 2017), and bibliographic lists of recent, relevant SLRs and meta-analyses were searched for studies of interest.
- **Study Selection:** Studies eligible for inclusion in the SLR were RCTs reporting the efficacy and/or safety of 2LT with antiangiogenic therapy (ramucirumab or nintedanib), immune checkpoint inhibitors (atezolizumab, avelumab, durvalumab, nivolumab, or pembrolizumab), or chemotherapy (docetaxel, gemcitabine, nab-paclitaxel, paclitaxel, pemetrexed, or vinorelbine) in patients with advanced NSCLC who have characteristics associated with aggressive disease (AD).
- **Aggressive Disease Definition:** Six potential overarching categorizations of characteristics associated with AD (based on expert clinical opinion) were explored:
  1. Refractory and/or progressive disease as best response to prior treatment
  2. Rapid progression
  3. Short duration on previous treatment
  4. High tumor burden or size, or "bulky disease"
  5. Short duration since start of last treatment
  6. High symptom burden

RESULTS

- A total of 22 publications reporting data from 14 RCTs investigating any of the interventions of interest, either as combination therapy or monotherapy and in at least one arm were identified for inclusion in the SLR.
- The 14 identified studies had one or more subgroups within five of the six categorizations (11, 2, 1, 2, and 4 studies presented subgroups within categories 1-5, respectively; Table 1).
- No RCTs presenting a subgroup of patients for category 6 were identified.
- Within each category, the identified subgroup definitions varied (15, 4, 3, 2, and 7 definitions within categories 1-5, respectively; Table 1).
- Three studies presented subgroup analyses of patients with AD further categorized by histology (6 subgroup definitions) or by ethnicity (2 subgroup definitions) (Table 1).
- Reporting of whether a subgroup was prespecified or not was limited and often unclear; 6 studies indicated that subgroup analyses of patients with AD characteristics were preplanned, prespecified, or predefined (Table 1).
  - Two of these studies also presented exploratory subgroup analyses using an alternative definition of AD.
  - A further three studies indicated that their subgroup analyses of patients with AD characteristics were exploratory.
- Moreover, baseline characteristics for the subgroup of patients with AD were often not reported.
- Studies often did not report subgroup data for all efficacy and safety outcomes included in the primary analysis of the entire study population. Across the SLR, outcome data by subgroup definition varied considerably (Table 2). Survival estimates were most commonly reported, with overall survival data available in 11 studies,[3-21] and progression-free survival data available in 8 studies.[6-16,21-24]
  - Response and safety data were available for only 2 studies.[7-14,21]
  - Comparable outcome data from more than one study were available for only three subgroup definitions (Table 2).

Table 1. Subgroup Definitions by Study and AD Characteristic Categorization

		AD Characteristic Categorization				
Study	**Interventions Investigated**	**Refractory and/or PD as Best Response to Prior Treatment**	**Rapid Progression**	**Short Duration on Previous Treatment**	**High Tumor Burden or Size**	**Short Duration Since Start of Last Treatment**
ASCEND-5[22]	• Ceritinib (750 mg) • Chemotherapy (pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2)	• No previous response (CR or PR) to crizotinib[a]			• Baseline SOD for target lesions larger or equal to median SOD[a]	
GFPC 10.02 study[23]	• Erlotinib (150 mg) + docetaxel (75 mg/m^2) • Docetaxel (75 mg/m^2)	• Refractory disease[b]				
Hanna et al., (2004)[20]	• Pemetrexed (500 mg/m^2) • Docetaxel (75 mg/m^2)					• < 3 months since 1LT
Heist et al., (2014)[18]	• Docetaxel (75 mg/m^2) + plinabulin (20 mg/m^2 or 30 mg/m^2) • Docetaxel (75 mg/m^2)				• Large lung tumors (> 3 cm) and 1 prior therapy	
INTEREST[3]	• Gefitinib (250 mg) • Docetaxel (75 mg/m^2)	• Refractory to previous platinum-based therapy[c] • Refractory to previous paclitaxel-based therapy[c] • PD best response to previous chemotherapy[c]				
ISEL[4,5]	• Gefitinib (250 mg) • Placebo	• Refractory to last chemotherapy[a] • PD/NE best response to most recent chemotherapy[a] • Asian patients with PD/NE as best response to most recent chemotherapy[b] • Asian patients whose disease was refractory to last chemotherapy[b]				
Li et al. (2014)[6]	• Erlotinib (150 mg) • Pemetrexed (500 mg/m^2)	• PD best response to 1LT[b]				
LUME-Lung 1[7,8,21]	• Docetaxel (75 mg/m^2) + nintedanib (200 mg) • Docetaxel (75 mg/m^2)	• PD best response to 1LT[d] • Adenocarcinoma and PD best response to 1LT[b]				• < 9 months since start of 1LT[b] • Adenocarcinoma and < 9 months since start of 1LT[b] • Adenocarcinoma and < 6 months since start of 1LT[a]
REVEL[9-14]	• Docetaxel (75 mg/m^2) + ramucirumab (10 mg/kg) • Docetaxel (75 mg/m^2)	• PD best response to 1LT/refractory to 1LT[b] • Adenocarcinoma refractory to 1LT[b]	• ≤ 9 weeks of 1LT until progression[b] • ≤ 12 weeks of 1LT until progression[b] • ≤ 18 weeks of 1LT until progression[b]	• ≤ 4 weeks of 1LT[b] • ≤ 8 weeks of 1LT[b] • ≤ 12 weeks of 1LT[b]		• < 9 months since start of 1LT[b] • Nonsquamous and < 9 months since start of 1LT[b] • Adenocarcinoma and < 9 months since start of 1LT[b] • Squamous and < 9 months since start of 1LT[b]
Schuette et al., (2005)[18]	• Docetaxel (75 mg/m^2) • Docetaxel (35 mg/m^2) weekly		• ≤ 3 months progression-free interval after 1LT[b]			
TAILOR[15]	• Docetaxel (75 or 35 mg/m^2) • Erlotinib (150 mg)	• PD best response to 1LT				
Takeda et al. (2016)[24]	• Docetaxel (60 mg/m^2) + bevacizumab (15 mg/kg) • Docetaxel (60 mg/m^2)	• SD/PD best response to 1LT				• < 6 months since start of 1LT
V-15-23[16]	• Gefitinib (250 mg) • Docetaxel (60 mg/m^2)	• PD/NE/unknown best response to prior chemotherapy[a]				
Wen et al. (2016)[17]	• Docetaxel (75 mg/m^2) + tamoxifen 80 mg • Docetaxel (75 mg/m^2)	• PD best response to 1LT				

1LT = first-line therapy; AD = aggressive disease; CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease; SOD = sum of diameters.

[a] Preplanned subgroup analysis.
[b] Exploratory subgroup analysis.
[c] Prespecified subgroup analysis.
[d] Predefined subgroup analysis.

Table 2. Number of Studies Reporting Efficacy and Safety Outcomes by AD Characteristic

	Aggressive Subgroup	OS	PFS	ORR	CR	PR	SD	PD	AE
Refractory/PD as best response to prior treatment	No previous response (CR or PR) to crizotinib		●						
	Refractory disease		●						
	Refractory to previous platinum-based therapy	●							
	Refractory to previous paclitaxel-based therapy	●							
	PD best response to previous chemotherapy	●							
	Refractory to last chemotherapy	●							
	PD/NE best response to most recent chemotherapy	●							
	PD best response to 1LT	●●●●	●●●						
	PD best response to 1LT/refractory to 1LT	●	●	●	●	●	●		●
	Adenocarcinoma refractory to 1LT	●	●						●
	SD/PD best response to 1LT		●						
	PD/NE/unknown best response to prior chemotherapy	●	●						
	Adenocarcinoma and PD best response to 1LT	●	●						
	Asian patients whose disease was refractory to last chemotherapy	●							
	Asian patients with PD/NE best response to most recent chemotherapy	●							
Rapid progression	≤ 9 weeks of 1LT until progression	●	●	●					●
	≤ 12 weeks of 1LT until progression	●	●	●					●
	≤ 18 weeks of 1LT until progression	●	●	●					●
	≤ 3 months progression-free interval after 1LT	●							
Short duration on first-line or previous treatment	≤ 4 weeks of 1LT	●	●	●					
	≤ 8 weeks of 1LT	●	●	●					
	≤ 12 weeks of 1LT	●	●	●					
Tumor burden or size, or bulky disease	Disease burden: baseline SOD for target lesions larger or equal to median SOD		●						
	Large lung tumors (> 3 cm) and one prior therapy	●							
Time/duration since initiation of last treatment	< 3 months since 1LT	●							
	< 6 months since start of 1LT		●						
	< 9 months since start of 1LT	●●	●●						
	Adenocarcinoma and < 9 months since start of 1LT	●●	●●	●	●	●	●	●	●
	Adenocarcinoma and < 6 months since start of 1LT	●	●						
	Nonsquamous and < 9 months since start of 1LT	●	●						
	Squamous and < 9 months since start of 1LT	●	●						

● = one study with outcome data reported; AE = adverse event; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

CONCLUSIONS

- Definitions of AD varied, both across the identified studies of 2LTs and within the predetermined categorizations, with refractory being the most frequent followed by short duration since start of last treatment. Moreover, only a few trials reported similar outcome data for the same AD subgroup, limiting the ability to compare outcomes across trials.
- With the emerging clinical importance of AD, more standard use of these definitions within RCTs may allow for greater comparison across 2LTs and will enable indirect treatment comparisons of the results.
- As with any subgroup, clarity on preplanned versus post hoc analysis is important for interpretation and should be specified.
- Additional studies powered to assess treatment benefits in patients with advanced NSCLC with AD are needed.

References:

See handout for references.

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