Second-Line Chemotherapy and Beyond for Non–Small Cell Lung Cancer

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KEYWORDS

• Non–small cell lung cancer • Chemotherapy • Second-line treatment • Docetaxel • Pemetrexed • Erlotinib

KEY POINTS

- Docetaxel, pemetrexed, and erlotinib are approved for the second-line treatment of NSCLC.
- The discovery of targetable mutations, the increasing use of maintenance strategies, and the introduction of immunotherapies has made the choice of second-line agents much more complicated.
- Ramucirumab with docetaxel is the only combination regimen that has shown improved overall survival in the second-line setting.
- Erlotinib is the only agent approved in the third-line setting for EGFR wild-type patients.

FIRST-LINE TREATMENT

In patients without targetable genetic alterations, the standard first-line therapy for advanced (stage IIIB or IV) non–small cell lung cancer (NSCLC) is chemotherapy with a platinum doublet for four to six cycles with or without bevacizumab.[1] Historically, several drugs including paclitaxel, docetaxel, gemcitabine, and vinorelbine were considered acceptable platinum partners in the first-line metastatic setting with essentially no differences in progression-free survival (PFS) or overall survival (OS). More recently, additional agents have been approved in combination with platinum in this setting including pemetrexed and nab-paclitaxel.[1–3] One particular advance in the last decade has been the recognition that histology should be considered in the choice of initial chemotherapy. This was discovered after an additional analysis of two studies showed pemetrexed to be more effective in nonsquamous histologies and less active in squamous tumors.[3–5] Based on these findings, the choice of first-line agents in metastatic NSCLC is now strongly based on presenting histology, and this initial choice affects available second-line options.

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MAINTENANCE THERAPY

Historically, patients treated with first-line platinum doublet chemotherapy who had objective responses or stable disease were placed on surveillance following completion of four to six cycles. However, over the last decade, new data suggests that there is benefit to the addition of maintenance therapy following initial chemotherapy. There are two maintenance strategies including continuation of an agent used in the first-line setting or switching to a previously unused agent (switch maintenance). There are data supporting the use of bevacizumab, pemetrexed, and erlotinib in the maintenance setting either as single agents or in combination.[6–11] Prior maintenance therapy is of particular importance when discussing second-line chemotherapy options because the use of maintenance therapy, particularly when switch maintenance is used, influences the availability of agents in the second-line setting and beyond.

CHEMOTHERAPY AS SECOND-LINE TREATMENT

Historically, nearly all patients received platinum doublet chemotherapy followed by single-agent chemotherapy in the second-line setting. However, with the discovery of targetable mutations, the development of tyrosine kinase inhibitors (TKI), the increasing use of maintenance strategies, and the introduction of immunotherapies to the current list of approved medications, choosing an appropriate second-line therapy has become more complicated. In general, those patients treated with targeted therapies receive a platinum doublet at the time of progression. For those who are wild-type for exploitable mutations, immunotherapy has become an increasingly popular second-line option because of its tolerability and potential for durable responses. However, there remains a role for additional treatments following second-line platinum doublets or immunotherapy, or alternatively, a role for second-line chemotherapy in those with contraindications to immunotherapy. This article discusses the available data for chemotherapy in the second-line treatment of NSCLC and beyond.

CHEMOTHERAPY IN THE SECOND-LINE SETTING AND BEYOND

With the exception of immunotherapy, there are four Food and Drug Administration (FDA)–approved agents for the second- and third-line treatment of advanced or metastatic NSCLC: (1) docetaxel, (2) pemetrexed, (3) erlotinib, and (4) ramucirumab. Docetaxel was the first agent approved for second-line treatment in 1999, and pemetrexed was approved in the second-line setting in 2004. Erlotinib was also approved in 2004 for second- and third-line treatment of advanced NSCLC and is currently the only FDA-approved third-line therapy. Ramucirumab was approved in 2014 in combination with docetaxel following progression on platinum-based chemotherapy.

SINGLE AGENT VERSUS COMBINATION REGIMENS

In the first-line setting, doublet chemotherapy is clearly superior to single-agent treatment in advanced NSCLC. However, it is unclear whether combination therapy in the second-line setting improves outcomes over single-agent chemotherapy. A meta-analysis of six trials compared combination regimens with single-agent therapy in the second-line setting. The combination arm showed a statistically significant improvement in response rate (RR) (15.1% vs 7.3%; $P = .0004$) and median PFS (14 weeks vs 11.7 weeks; $P = .0009$; hazard ratio [HR], 0.79) compared with single-agent therapy. However, there was no difference in median OS between the two groups (37.3 weeks vs 34.7 weeks; HR, 0.92; $P = .32$). The doublet arms had significantly higher rates of grade 3/4 hematologic (41% vs 25%; $P<.0001$) and