Pathways to improving combined modality therapy for stage III nonsmall-cell lung cancer

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Received 22 September 2015; revised 4 December 2015; accepted 14 December 2015


Materials and methods: Although the majority of patients are not cured with currently available therapies, there have been significant improvements in stage-specific outcomes over time [Videtic G, Vokes E, Turrisi A et al. The survival of patients treated for stage III non-small cell lung cancer in North America has increased during the past 25 years. In The 39th Annual Meeting of the American Society of Clinical Oncology, ASCO 2003, Chicago, IL. Abstract 2557. p. 291]. This review focuses on past progress and ongoing research in the treatment of locally advanced, inoperable nonsmall-cell lung cancer (NSCLC).

Results: In the past, randomized trials revealed advantages to the use of thoracic radiotherapy (TRT) and then, the addition of induction chemotherapy. This was followed by studies that determined concurrent chemoradiotherapy to be superior to sequential therapy. A recent large phase III trial found that the administration of 74 Gy of conventionally fractionated photon-based TRT provided poorer survival than did the standard 60 Gy. However, further research on other methods of applying radiotherapy (hypofractionation, adaptive TRT, proton therapy, and stereotactic TRT boosting) is
proceeding and may improve outcomes. The molecular characterization of tumors has provided more effective and less toxic targeted treatments in the stage IV setting and these agents are currently under investigation for earlier stage disease. Similarly, immune-enhancing therapies have shown promise in stage IV disease and are also being tested in the locally advanced setting.

**Conclusion:** For locally advanced, inoperable NSCLC, standard therapy has evolved from TRT alone to combined modality therapy. We summarize the recent clinical trial experience and outline promising areas of investigation in an era of greater molecular and immunologic understanding of cancer care.

**Key words:** nonsmall-cell lung cancer, review, targeted therapy, radiation therapy, chemotherapy, immunotherapy

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**introduction**

**thoracic radiotherapy becomes standard therapy**

In 1966, Wolf et al. reported on a Veterans’ Administration Hospital phase III trial that randomly assigned 554 patients, with localized, clinically inoperable lung cancer of all histologies, to either thoracic radiotherapy (TRT) or placebo (lactose tablets) [1, 2]. Doses ranged from 4000 to 5000 r with daily doses of 150–200 r. The median survival of patients given TRT was 142 days when compared with 112 days ($P = 0.05$) for those who received the placebo. This trial helped establish the role of TRT for locally advanced inoperable lung cancers.

**sixty gray in 30 fractions becomes standard of care for TRT**

The Radiation Therapy Oncology Group (RTOG/NRG) performed a phase III trial (7301, $n = 383$) designed to assess the effect of radiation dose fractionation on outcome comparing 40 Gy/10 fractions (split course), 40 Gy/20 fractions, 50 Gy/25 fractions, and 60 Gy/30 fractions. No chemotherapy was given. Chest X-rays were used to determine the intrathoracic failure rates that occurred in 48% with 40 Gy, 38% with either 40 Gy (split course) or 50 Gy, and 27% with 60 Gy ($P = 0.04$). Although the differences in survival were not significant, this study was used to define the standard RT dose in as 60 Gy/30 daily fractions based on the improved local control. Today, we would consider chest X-ray determination of local control as suboptimal. Conventional RT alone resulted in a median survival of 10 months and a 5-year survival rate of 5% [3].

**the combination of chemotherapy plus radiation is superior to TRT alone**

In the 1970s and 1980s, early phase trials established the feasibility of administering two to three cycles of induction chemotherapy using cisplatin-based chemotherapy. In a randomized phase III trial, the Cancer and Leukemia Group B (CALGB-8433/ALLIANCE, $n = 155$) found that two cycles of cisplatin and vinblastine induction chemotherapy followed by conventional TRT (60 Gy/30 fractions) beginning on day 50 yielded significantly better survival than the identical TRT alone. The median survival and 5-year survival rates were 13.7 months and 17% for the combined therapy versus 9.6 months and 6% for TRT alone ($P = 0.012$) [4, 5]. The main finding, that combined chemotherapy and TRT was superior to TRT alone, was confirmed in subsequent larger phase III trials [6–8]. The superiority of chemoradiotherapy (CRT) compared with TRT alone was also confirmed in elderly patients by Atagi et al. [9].

**concurrent chemoradiotherapy is superior to sequential therapy**

Furuse et al. carried out a randomized trial comparing sequential with concurrent therapy ($n = 320$) [10]. In the concurrent arm, chemotherapy consisted of mitomycin C, vindesine, cisplatin, and TRT at a dose of 56 Gy (2 Gy/fraction with a break). In the sequential arm, the same chemotherapy was given, but TRT began after completing chemotherapy and included 56 Gy (2 Gy/fraction without a break). The median survival was better with concurrent therapy (16.5 months) than sequential therapy (13.3 months) ($P = 0.04$). The 5-year survival rates with concurrent therapy were 15.8 and 8.9% with sequential therapy. A meta-analysis was also carried out based on data from six randomized trials ($n = 1205$) [11]. There was a significant survival benefit from concurrent chemoradiotherapy [hazard ratio (HR) = 0.84; $P = 0.004$], with an absolute benefit of 4.5% at 5 years. Concurrent therapy also increased severe (grades 3–4) acute esophageal toxicity from 4% to 18% ($P < 0.001$) [10, 12–16]. Concurrent therapy is recommended for patients robust enough to tolerate it safely.

**involved field TRT appears better than TRT employing elective nodal irradiation**

Elective nodal TRT includes treating adjacent nodal regions without evidence of adenopathy as a prophylactic therapy for presumed metastatic disease that cannot be radiologically detected whereas involved field TRT treats only enlarged or hypermetabolic lymph nodes. Chen et al. reported the results of a phase III study ($n = 99$) comparing concurrent chemotherapy (carboplatin and paclitaxel) and either involved field radiotherapy (IF-TRT; median dose: 60 Gy/30) or elective nodal irradiation (ENI; median dose: 60 Gy/30) for locally advanced nonsmall-cell lung cancer (NSCLC). They found that IF-TRT did not increase the risk of nodal/regional failures. The median survival was 27.8 months with IF-TRT arm and 16.7 months with ENI. The 3-year survival rates were 36.6% with IF-TRT versus 30.3% with ENI ($P = 0.08$) [17]. This difference (10.9 months) in median survival is similar in magnitude to the reported survival differences in trials that employed concurrent chemotherapy with ENI-TRT compared with those that employed IF-TRT [18–20]. There does appear a trend to better survival with IF-TRT. This may be due to decreased dose delivery to the critical surrounding normal structures such as lungs and heart.
RTOG-0617 establishes that 60 Gy in 30 daily fractions is better than 74 Gy in 37 fractions

RTOG-0617 tested two hypotheses: first, higher doses of TRT would provide better survival than conventional TRT doses and second, cetuximab [an epidermal growth factor receptor (EGFR) inhibitor] would improve survival when added to chemoradiotherapy [19]. All patients (n = 544) received standard chemotherapy consisting of concurrent TRT plus paclitaxel and carboplatin followed by two cycles of paclitaxel and carboplatin. Patients were randomized to either 60 Gy (standard-dose) or 74 Gy (high-dose), and in a second randomization (2 × 2 factorial design) 60 Gy plus cetuximab, or 74 Gy plus cetuximab. TRT included IF-TRT with either 3-D TRT or intensity modulated radiotherapy (IMRT). The median survival was 28.7 months with standard-dose TRT and 20.3 months with high-dose TRT (HR = 1.38, P = 0.004). The median survival in patients who received cetuximab was 25 months compared with 24 months in those who did not (HR = 1.07, P = 0.29). The authors concluded that the addition of cetuximab provided no survival benefit and that standard TRT dose should remain 60 Gy/30 fractions. One important finding was the influence of heart dose on survival. In the multivariate analysis of survival, greater heart exposure was associated with poorer survival and patients receiving 74 Gy had significantly higher heart doses. Additionally, the favorable results in 60 Gy arm occurred in the PET era where better selection of patients without metastases at baseline and targeting of their lesions may have contributed to the high median survival. Although 60 Gy/30 daily fractions was concluded to be standard fractionation, there are little data available regarding differences in survival within the range of doses between 60 and 72 Gy. In recent years, it has also become increasingly clear that the quality of the treatment plan and its careful execution can influence outcomes. Of particular interest are data that demonstrate centers with a higher volume of stage III patients treated achieve better survival and had a trend to lower toxicity [21]. This suggests that these challenging multimodality treatment plans and the close coordination of care they require should be performed at centers with an experienced team whenever possible.

Multiple daily fractions appear to offer a small but significant advantage. This could be exploited in future

Randomized trials assessing multiple daily fractions [hyperfractionation or accelerated (modified) fractionation] TRT offered conflicting results regarding influence on survival [22, 23]. The Meta-Analysis of Radiotherapy in Lung Cancer (MAR-LC) Collaborative Group carried out a meta-analysis in patients with nonmetastatic NSCLC. Included were trials comparing modified TRT with a conventional TRT (1.8–2 Gy fraction with a minimum dose of 60 Gy) for NSCLC. In the analysis of NSCLC that included 8 trials with 1594 patients, modified TRT improved survival compared with conventional TRT (HR = 0.87, P = 0.009], resulting in an absolute benefit of 3% at 5 years. Modified TRT also increased acute esophageal toxicity (HR = 2.11, P = 0.001) but did not impact hematological, pulmonary, or cardiac toxicity. Patients appeared to benefit from modified TRT in terms of survival but did suffer more esophagitis.

The addition of induction or consolidation chemotherapy or other antineoplastic agents to concurrent chemoradiotherapy lent support to the continued use of concurrent platinum-based doublet therapy during TRT

Since both concurrent chemoradiotherapy and induction chemotherapy were shown superior to radiotherapy alone and in turn the concurrent approach superior to induction chemotherapy, there has been debate concerning the optimal number of chemotherapy cycles. Typically, during concurrent chemoradiotherapy, only two to three cycles of chemotherapy are administered, in some regimens at systemically active doses (cisplatin/etoposide) and in others at lower weekly doses that may be less active systemically. As a result, the addition of induction chemotherapy to concurrent chemoradiotherapy and the addition of consolidation chemotherapy following concurrent chemoradiotherapy were investigated. CALGB-39801 demonstrated that the addition of induction chemotherapy did not improve survival [24]. Similarly, consolidation chemotherapy (docetaxel) added to cisplatin/etoposide and concurrent radiotherapy did not improve outcomes [25]. This was confirmed by Ahn et al. investigating weekly concurrent chemoradiotherapy followed by weekly low-dose cisplatin and docetaxel versus chemoradiotherapy alone. Progression-free survival (PFS) and overall survival were not statistically different between the two arms [26].

Several studies have explored whether an optimal chemotherapy regimen administered concurrently with radiotherapy can be defined. Cisplatin–etoposide and vinorelbine as well as weekly carboplatin–paclitaxel or MVP (mitomycin C, vindesine, cisplatin) have all been used. Multiple small comparative studies have been conducted [27–29]. While these studies were inconclusive, they did not report major differences with the exception of a small randomized phase II trial that directly compared cisplatin/etoposide and carboplatin/paclitaxel with concurrent radiotherapy. This trial suggested superiority for cisplatin/etoposide and this observation is currently being further investigated in a randomized phase III format [28]. A database review conducted in the United States showed very similar outcomes between patients treated with these two regimens [30]. Most recently, a large (n = 555) randomized phase III trial compared the cisplatin/etoposide radiotherapy standard with a cisplatin/pemetrexed concurrent radiotherapy regimen [31]. Both regimens were administered at systemic doses; consolidation chemotherapy was given on both study arms. The median overall survival times were 26.8 and 25 months, respectively (P > 0.05). However, the pattern of toxicity varied with more patients having severe adverse reactions on the etoposide arm (79% versus 68%) and a higher incidence of grades 3–4 neutropenia (29% versus 18%), grades 3–4 dysphasia was 5.9% and 6.7%, respectively. This and the other above trials suggest that current standards should support the use of platinum-based doublet therapy administered for two to three cycles during chemoradiotherapy.

Numerous approaches involving targeted agents have been investigated. These include the abovementioned addition of cetuximab to chemoradiotherapy in RTOG-0617. The addition of erlotinib or gefitinib did not result in superior outcomes. In particular, erlotinib administered following consolidation chemotherapy and concurrent chemoradiotherapy to a cohort of patients without
EGFR mutation status defined resulted in a significantly decreased survival [32]. Similarly, a randomized trial investigating the addition of thalidomide as an antiangiogenic compound showed no difference in survival. Other antiangiogenic factors (bevacizumab, AE-941) have also been shown toxic or ineffective when added to chemoradiotherapy [19, 32–37] (Table 1).

Tecemotide is a liposome-based MUC1 vaccine. MUC1 is a mucinous lipoprotein that is overexpressed in NSCLC. In an early phase clinical trial, the addition of this vaccine suggested a benefit. A large randomized trial looking at combined modality therapy (induction or concurrent chemoradiotherapy followed by placebo or tecemotide administration) showed no survival difference although, in subset analysis, patients receiving concurrent chemoradiotherapy appeared to have a survival benefit [38]. However, following further observations from a Japanese trial, further development of this drug in lung cancer has been halted.

**current trials and initiatives (the road to further progress)**

**targeted therapy for patients with stage III NSCLC and specific driver mutations is one avenue for future investigation**

The activation of specific receptors that control molecular pathways regulating tumor growth results in malignant cellular behavior. Mutations in the EGFR tyrosine kinase occur in ~15% of lung adenocarcinomas in the United States. EGFR tyrosine kinase inhibitors gefitinib, erlotinib, and afatinib significantly prolong PFS in stage IV NSCLC patients with activating mutation in EGFR compared with platinum-based chemotherapy. These agents had no definitive effect on overall survival in a meta-analysis including 23 eligible randomized trials [39], likely due to a cross-over effect although an updated analysis of the lung-lux 3 and 6 trials comparing afatinib with cisplatin pemetrexed or gemcitabine–cisplatin did show a survival advantage for patients with del19 EGFR mutations [40].

Another driver mutation involves the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion gene found in 2%–7% of NSCLC patients. An inhibitor of the product of this gene (ALK fusion kinase) is crizotinib that produced objective responses in 60.8% of patients harboring tumors with this specific mutation. The median duration of response was 49.1 weeks and 1-year survival rate was a respectable 74.8% [41].

Solomon et al. carried out a phase III trial comparing first-line therapy with either crizotinib or chemotherapy in stage IV, ALK-positive nonsquamous NSCLC patients. PFS was better with crizotinib than chemotherapy (median: 10.9 versus 7.0 months; \(P < 0.001\)). Objective response rates were better with crizotinib at 74% versus 45% with chemotherapy (\(P < 0.001\)). The 1-year survival was 84% with crizotinib versus 79% with chemotherapy (HR = 0.82; \(P = 0.36\)) [42].

On the basis of these findings, the RTOG/NRG and Alliance joined forces perform a randomized phase II study of individualized therapy for stage III NSCLC (RTOG 1306/ALLIANCE 31101). Patients with EGFR mutations are randomized to standard platinum-doublet therapy plus TRT (60 GY) versus induction erlotinib for 12 weeks followed by the same chemoradiotherapy. Patients with ALK translocations are randomly assigned to standard platinum doublet plus TRT (60 GY) versus induction crizotinib for 12 weeks followed by the same chemoradiotherapy. Additional targetable driver mutations have been defined (such as ROS1, met, raf, ret, and her-2) and might be evaluated in similar fashion although their low incidence likely would prohibit doing that in a randomized fashion.

**poly(ADP-ribose) polymerase inhibitors may have a role in lung cancer therapy**

Poly(ADP-ribose) polymerase (PARP) are DNA binding and repair proteins [43]. Many DNA errors occur during each cell cycle that require repair. DNA damage is the main mechanism of action of much chemotherapy and RT. The PARP inhibitors appear to enhance these cancer-killing effects and a randomized

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**Table 1. Select trials that tested targeted therapy for stage III NSCLC patients (without evidence of the targets’ presence in their tissue)**

<table>
<thead>
<tr>
<th>Study (author)</th>
<th>N</th>
<th>Arms</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>S0023 (Kelly, 2008)</td>
<td>243</td>
<td>Cisplatin and etoposide and TRT (61 Gy/1.8–2 Gy fx3) then: docetaxel ×3 then: gefitinib versus none</td>
<td>Median survival time = 23 months for gefitinib ((n = 118)) versus 35 months for placebo ((n = 125; \ P = 0.013)). The toxic death rate was 2% with gefitinib compared with 0% for placebo</td>
</tr>
<tr>
<td>RTOG0617 (Bradley, 2015)</td>
<td>544</td>
<td>Carboplatin/paclitaxel and TRT (60 Gy/30 versus 74G/37) × concurrent cetuximab followed by carboplatin/paclitaxel x2</td>
<td>Median survival: 24.0 months (no cetuximab) 25 months (cetuximab) (P = 0.29)</td>
</tr>
<tr>
<td>NTR2330 (Walraven, 2015)</td>
<td>102</td>
<td>Hypo-fractionated TRT (66 Gy/2–2.75 Gy fractions) and concurrent daily low-dose cisplatin versus identical treatment regimen and weekly cetuximab</td>
<td>Median survival: 33.0 months (no cetuximab) versus 30.0 months (cetuximab) (P = 0.36)</td>
</tr>
<tr>
<td>Spigel, 2009</td>
<td>5</td>
<td>Single-arm study of bevacizumab and pemetrexed and carboplatin and TRT (61.2/1.8 Gy fractions)</td>
<td>Tracheoesophageal fistula in 2 (40%) of 5 patients prompting closure of the study</td>
</tr>
<tr>
<td>NCT00531076 (Lind, 2012)</td>
<td>6</td>
<td>Two cycles of induction cisplatin-based doublet chemotherapy then: TRT: 66 Gy/33 fractions and concurrent bevacizumab</td>
<td>67% grade ≥2 radiation-induced lung injury = alarming, patients had low V20 values and no concurrent chemotherapy</td>
</tr>
<tr>
<td>S0533 (Wozniak, 2015)</td>
<td>21</td>
<td>Cisplatin and etoposide concurrent with radiotherapy (64.8 Gy/38 fractions) followed by docetaxel and bevacizumab</td>
<td>Grade 3 pneumonitis [2/21 (9.5%)] and 2/21 (9.5%) of grade 5 hemoptysis resulted in closure</td>
</tr>
</tbody>
</table>
phase II study comparing doublet chemotherapy with or without the PARP inhibitor, veliparib, in stage IV NSCLC patients demonstrated an increased PFS and phase III investigation is in progress. Southwest Oncology Group (SWOG) has opened a phase I–II trial (S1206), a dose-finding study followed by phase II randomized, placebo-controlled study of veliparib added to chemoradiotherapy with carboplatin and paclitaxel for unresectable stage III NSCLC. Patients receive chemoradiotherapy with or without veliparib. A similar trial is being performed within the ALLIANCE Cooperative Group seeking to also establish the maximum tolerated dose of veliparib when added to concurrent chemoradiotherapy.

**immunotherapy holds promise for stage III NSCLC**

The programmed cell death-1 (PD-1) receptor is present on T cells acting as an immune checkpoint. It downregulates the immune system by preventing the activation of T cells. Drugs that block PD-1 activate the immune system to attack cancer cells. Nivolumab is a fully human IgG4 PD-1 inhibitor antibody that impairs PD-1-mediated signaling restoring immunoreactivity [44]. Nivolumab and other PD-1 or PD-L1 inhibitors have shown consistent activity in NSCLC and are recently approved for use in the second-line setting for patients failing standard first-line therapy in the United States.

In the CheckMate-017 Trial [44], the median survival was 9.2 months with nivolumab versus 6.0 months with docetaxel (HR = 0.59; P < 0.001) in patients with squamous cell lung cancer. Patients had better survival, response rates, and PFS with nivolumab than with docetaxel, regardless of PD-L1 expression level and the agent was approved for use in the second-line setting by the FDA in the United States.

Similar findings occurred in the Checkmate-57 trial with nonsquamous NSCLC histologies [45]. Nivolumab demonstrated superior survival compared with docetaxel (median survival = 12.2 versus 9.4 months; P = 0.0015) (HR = 0.73; P = 0.0015). Severe (grades 3–5) toxicity occurred in 10.5% of nivolumab patients compared with 53.7% of docetaxel patients.

Additionally, Garon et al. reported a median survival of 12 months in a phase I trial of the PD-1 inhibitor, pembrolizumab, for advanced NSCLC [46]. PD-L1 expression in at least 50% of tumor cells correlated with improved pembrolizumab efficacy.

It is unclear how PD-1 or PD-L1 inhibitors will be optimally integrated into concurrent chemoradiotherapy. There is a concern that the simultaneous administration of radiotherapy could result in exacerbated pulmonary toxicity. Additionally, their administration with systemic chemotherapy (possibly with the use of dexamethasone) could result in an immunosuppressive effect limiting efficacy. The Alliance is initiating a trial that will investigate the neoadjuvant administration of a PDL-1 inhibitor. To decrease the risk of patients progressing before the administration of chemoradiotherapy, the patient cohort will be enriched with patients having PD-L1 expression. Another randomized phase III trial has been initiated, investigating consolidation therapy with MEDI4736 in the PACIFIC trial. Patients having completed concurrent chemoradiotherapy are randomized to MEDI4736 or placebo. RTOG/NRG is planning a similar trial randomizing patients prior to concurrent chemoradiotherapy to consolidation with nivolumab versus observation. These are the first trials investigating this new class of drugs in the stage III setting and will be followed with great interest.

**metformin has radiosensitizing properties and may be a useful therapy**

Metformin use was found to be associated with a decrease in lung cancer incidence in patients with diabetes [47]. Metformin was also found to be an effective radiosensitizing agent [48]. Additionally, metformin use was associated with better survival of diabetic patients with lung cancer [49, 50]. Heath Skinner (M.D. Anderson, personal communication) found that diabetics taking metformin had a median survival of 28 months compared with 16 months in those not taking metformin (P = 0.02). These findings led investigators to write NRG-LU001 (randomized phase II trial of concurrent chemoradiotherapy ± metformin HCL in locally advanced NSCLC). Other drugs that have been re-purposed for the lung cancer therapy in the research setting include statins, β-blockers, itraconazole, and NSAIDs [51].

**current avenues of radiotherapy research may improve TRT**

Dose intensification is an area of active research to improve the therapeutic index of TRT. Very simply, more radiation dose delivered in less time may improve local control and survival if the dose distribution is favorable with the tumor receiving the greatest dose while sparing normal tissues. This can be quantified by calculating the biologically effective dose. The details can be found in Schild et al. [52]. Other recent technical improvements include image guidance and motion management systems.

**adaptive radiotherapy employing advanced imaging may improve outcomes**

Tumors often shrink during the course of TRT and the treatment plans can be altered to adapt to these changes in tumor size and contour. This can be advantageous in allowing small volumes of residual tumor to be treated to greater doses without exceeding the tolerances of the surrounding normal tissues. The goal is to achieve better disease control safely. RTOG1106 is a randomized phase II trial including concurrent chemotherapy (paclitaxel/ carboplatin) plus either standard TRT (60 Gy/30 fractions) or adaptive TRT. The adaptive program includes 46.2 Gy/21 fractions followed by positron emission tomography (PET)/computed tomography (CT) plus an additional 19.8–34.2 Gy/9 fraction boost to remaining PET avid regions while maintaining a mean lung dose of ≤20 Gy. It is hoped that adaptive TRT will provide better outcomes by boosting only the remaining hypermetabolic tumor.

**Hypofractionation (delivering larger but fewer fractions in less overall time) shows promise**

Hypofractionation has been examined as a method of dose-intensification in several trials (Table 2) [35, 53–62]. One very promising phase II trial (NTR2230) included 66 Gy/24–2.75 Gy fractions with daily cisplatin (6 mg/m²) ± cetuximab for stages II and III patients. Cetuximab did not influence survival. However, the median survival and 5-year survival rate of the cisplatin-RT arm were very favorable at 33 months and 37%, respectively [35, 61].
<table>
<thead>
<tr>
<th>First author, year</th>
<th># of patients/stages</th>
<th>Chemotherapy</th>
<th>Fractionation</th>
<th>Trial phase</th>
<th>Median OS (months)</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belderbos, 2007</td>
<td>158/I–III</td>
<td>IND GEM/CIS then TRT versus daily CIS during TRT</td>
<td>66 Gy/24</td>
<td>3</td>
<td>16.2 versus 16.5</td>
<td>This trial was closed prematurely due to poor accrual. Survival was similar with IND versus CON CHEMO. HEME toxicity greater in sequential arm. Esophagitis was greater in concurrent arm.</td>
</tr>
<tr>
<td>Tsoutsou, 2008</td>
<td>14/III–IV</td>
<td>VINO and liposomal DOXO with increasing doses of VINO</td>
<td>52.5 Gy/15</td>
<td>1</td>
<td>8</td>
<td>Acceptable tolerance noted when the dose of VINO ≤25 mg/m².</td>
</tr>
<tr>
<td>Bral, 2010</td>
<td>34/III</td>
<td>CON DOCE/CIS</td>
<td>60 Gy/30–74.4 Gy/30</td>
<td>1/2</td>
<td>17.9</td>
<td>MTD = 67.2 Gy/30</td>
</tr>
<tr>
<td>Matsuura, 2009</td>
<td>10/III</td>
<td>Weekly CARBO/paclitaxel</td>
<td>62.5–70 Gy, median: 65 Gy in 2.5 Gy fxS</td>
<td>2</td>
<td>27.5</td>
<td>There were no local failures at 67.5 Gy or greater dose. There was no grade 4/5 toxicity.</td>
</tr>
<tr>
<td>Casas, 2011</td>
<td>32/III</td>
<td>Paclitaxel(P)/CARBO (C) then P-TRT then P&amp;K</td>
<td>61.64 Gy/23–2.68 Gy fxS</td>
<td>2</td>
<td>16.9</td>
<td>1 grade 4 heme and 1 grade 5 nonheme toxicity. 'Acceptable results with acceptable toxicity'</td>
</tr>
<tr>
<td>Maguire, 2012, 2014</td>
<td>130/III</td>
<td>CON versus SEQ CIS/VINO</td>
<td>55 Gy/20 fxS</td>
<td>3</td>
<td>24.3 (con) 18.4 (seq)</td>
<td>Toxicity was acceptable and similar in both arms. Local relapse was 10% in the CON and 22% in the SEQ arms. QOL was not significantly different. Authors felt results quite favorable compared with other RCTs.</td>
</tr>
<tr>
<td>Lin, 2013</td>
<td>27/III or REC 102</td>
<td>CON VINO and CARBO CON CIS (arm A) versus CON CIS + cetuximab (arm B)</td>
<td>66, 69 and 72 Gy in 3 Gy fxS</td>
<td>1</td>
<td>13</td>
<td>69 Gy was regarded as the MTD. Cetuximab conferred no survival benefit but did increase toxicity.</td>
</tr>
<tr>
<td>Van den Heuvel, 2014 and Walraven, 2015</td>
<td>102</td>
<td>CON VINO and CARBO CON CIS (arm A) versus CON CIS + cetuximab (arm B)</td>
<td>66 Gy/24</td>
<td>2</td>
<td>33 months (A) 30 months (B)</td>
<td></td>
</tr>
<tr>
<td>Bearz, 2013</td>
<td>37</td>
<td>IND CIS + DOCE Then CON DOCE in increasing doses</td>
<td>60 Gy/25</td>
<td>1</td>
<td>24 of 33 patients completing treatment</td>
<td>CON weekly DOCE and tomotherapy are feasible, and even with DOCE at 38 mg/m²/week, there was no limiting toxicity.</td>
</tr>
</tbody>
</table>

CIS, cisplatin; DOCE, docetaxel; DOXO, doxorubicin; CON, concurrent; GEM, gemcitabine SEQ, sequential; IND, Induction; VINO, vinorelbine; SEQ, sequential; CHEMO, chemotherapy; HEME, hematologic; RCTs, randomized controlled trials.
stereotactic body radiation therapy has been extensively explored for early NSCLC

Investigators have also used this therapy as a boost following conventional chemoradiotherapy. Trial results are too preliminary to estimate median survival [63, 64].

proton therapy shows promise in improving TRT

Protons interact with tissues and are absorbed differently than do X-rays (photons), the conventional radiation used to treat lung cancer. Photons have neither mass nor charge. Thus, an X-ray beam enters a patient’s body and traverses it from the entrance point, traveling in a straight line and exiting the other side. Prior to entering the tumor, cell-killing energy is absorbed within the normal tissues and peaks in the body at a depth determined by the energy of the beam and, then, slowly decreases as it traverses the body and exits. In contrast, protons have mass and charge. The mass gives momentum to the accelerated particles and the charge acts like a brake to the moving protons within the body. The protons enter the patient and start slowing down, giving up a small fraction of energy to the surrounding tissues until they get to a critical depth at which they release all of the remaining energy within a very short distance and stop. This depth is determined by the kinetic energy imparted upon the proton by the acceleration system (cyclotron or synchrotron). The majority of the cancer-killing energy is transferred to the tissues by the protons and this occurs in a small region within a tumor. Since the protons have stopped, there is no dose given to the tissues beyond the tumor. There is a much greater fraction of the cell-killing energy imparted on the entrance and exit both to and from the tumor by a photon beam than a proton beam. This results in better radiotherapy plans where a greater fraction of the cell-killing energy is deposited within the tumor. For example, if one treats a tumor and adenopathy anterior to the esophagus with photons, patients frequently get esophagitis due to the exit of beam through the esophagus. However, a proton beam directed from the anterior direction posteriorly can treat this same tumor and stop before the esophagus resulting in a lower dose and risk of esophagitis. This same principle can be used to better spare lung, bone marrow, and heart with proton plans (Figure 1B).

Sejpal et al. carried out a comparison of patients treated with either proton or photon therapy [65]. The median dose was 74 Gy with protons versus 63 Gy with photons. Rates of severe (grade ≥ 3) pneumonitis and esophagitis in the proton group (2% and 5%, respectively) were lower despite the higher radiation dose (3D-CRT, 30% and 18%; IMRT, 9% and 44%; P < 0.001 for all). The median survival was 17.7 months with photons compared with 24.4 months for protons (P = 0.1). However, the number of patients was too small to have the power to detect a 6-month advantage in survival. They found that higher doses of proton radiation could be delivered to lung tumors with a lower risk of esophagitis and pneumonitis. A randomized phase II trial of chemotherapy plus either photon or proton TRT is underway at MD Anderson Cancer Center and a similar phase III trial is being performed by NRG (RTOG-1308).

Currently, much controversy exists regarding proton therapy. This is not based on the physics that favors protons in providing better dose-distributions but rather the current absence of definitive comparative clinical data and financial cost. However, the cost of facilities is coming down with smaller one-room facilities. At Mayo Clinic, the decision has been made to charge commercial patients the same amount for both proton therapy and IMRT. In spite of increased cost of proton therapy, it has

Figure 1. (A) Dosimetry for proton (left) versus photon (right) dosimetry for a lung malignancy behind the heart. Sixty-six gray is the prescribed dose. The first axial image includes pencil beam proton therapy from multiple beams entering from the posterior aspect of the patient. At the right is the same patient treated with rotational IMRT and beams entering from 360°. The region receiving 20 Gy or greater is contained within the outermost isodose line. The IMRT (photon) plan exposes the surrounding normal heart and lung tissue to more radiation than the proton plan. The protons stop prior to irradiating most of the heart. On the basis of the findings of RTOG 0617, greater heart dose correlated with significantly lower survival. (B) The color-wash representation of the same data.
been shown cost-effective due to decreased long-term toxicity in specific situations [66, 67]. Further research will determine whether protons will provide meaningful and cost-effective improvements in lung cancer therapy.

**conclusion**

Lung cancer is the most common cause of cancer-related deaths and attempts to prevent this by ridding society of tobacco smoking have not yet changed this fact. This review focused on past progress and ongoing research in the treatment of locally advanced, inoperable NSCLC. Significant improvements in care include the use of moderate dose (60 Gy/30 fractions) photon TRT administered concurrently with platinum-based therapy. However, further research on methods of dose-intensification (hypofractionation, adaptive TRT, stereotactic TRT boosting) is proceeding and may improve outcomes. Proton beam therapy has the potential to provide improvement in the TRT of lung cancer by decreasing the integral dose within the body and better sparing the critical surrounding organs (heart, lungs, bone marrow, esophagus). Randomized trials comparing proton beam therapy and adaptive TRT with conventional photon-based TRT are being performed to clarify their roles. Modern molecular and immunologic research has provided more effective and less toxic targeted treatments in the stage IV setting that are currently under investigation for locally advanced NSCLC. Research in an era of greater molecular and immunologic understanding will provide meaningful improvements in the care of NSCLC patients.

**disclosure**

EEV: consult/advisory role for AbbVie, Agen, AstraZeneca, Boehringer-Ingelheim, Celgene, Eisai, Eli Lilly, Genentech, Merck, Synta, and VentiRx. SES: none declared.

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IDH mutations in cancer and progress toward development of targeted therapeutics

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Received 6 October 2015; revised 23 December 2015; accepted 24 December 2015

Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) are key metabolic enzymes, converting isocitrate to α-ketoglutarate (αKG). IDH1 and IDH2 mutations have been identified in multiple tumor types, including gliomas and myeloid malignancies such as acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). Here we provide an overview of the function of normal and mutated IDH, discuss the role of IDH mutations in tumorigenesis and progression and review the key clinical considerations when treating IDH-mutated tumors based on emerging clinical data from mutant IDH1/2 inhibitor trials. IDH1 and IDH2 mutations confer neomorphic activity in the mutant protein, resulting in the conversion of αKG to the oncometabolite, D-2-hydroxyglutarate (2-HG). The subsequent accumulation of 2-HG results in epigenetic dysregulation via inhibition of αKG-dependent histone and DNA demethylases, and a block in cellular differentiation. There is growing preclinical and clinical evidence suggesting that IDH mutations are involved in neoplasia. Furthermore, preclinical studies assessing small molecule inhibitors of mutant IDH1/2 enzymes have provided proof of concept that this approach decreases intracellular 2-HG levels, reverses epigenetic dysregulation and induces cellular differentiation. Phase I studies of mutant IDH inhibitors are currently ongoing in patients with IDH-mutant hematologic and solid tumors, with early data in hematologic tumors suggesting a manageable safety profile as well as clinical benefit, with a mechanism of action based on differentiation of malignant cells. Inhibition of mutant IDH shows promise as a treatment approach in hematologic malignancies, with further development ongoing in solid tumors and glioma. The mutant IDH inhibitors may have clinical utility both as single agents and in combination strategies that target additional oncogenic pathways.

Key words: glioma, hematologic malignancy, isocitrate dehydrogenase, IDH1, IDH2, small molecule inhibitor

introduction

Among the most notable cancer genome-wide sequencing discoveries in recent years was the finding of mutation hot-spots in the isocitrate dehydrogenase (IDH) genes in grade II/III astrocytomas and oligodendrogliomas and in secondary glioblastomas (GBMs) [1, 2]. This was rapidly followed by identification of recurrent IDH1/2 mutations in acute myeloid leukemia (AML), myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) and cholangiocarcinoma [3–5], as well as in a rare aciduria [6, 7]. These genetic findings coincided with the emergence of therapeutic research based on the hypothesis that dysregulation of cellular energetics and metabolism is a hallmark of cancer [8]. Mutant IDH is now a therapeutic target of great interest in cancer research, especially in AML, given the limitations of current approved therapies and the encouraging early clinical data demonstrating proof of concept for investigational mutant IDH1/2 inhibitors. Here, we provide an overview of the function of normal and mutated IDH, discuss the role of IDH mutations in tumorigenesis and progression and review key clinical considerations when treating IDH-mutated tumors based on emerging clinical data from mutant IDH1/2 inhibitor trials.

normal functions of IDH in homeostasis

The IDH family comprises three isozymes (IDH1, IDH2 and IDH3) that convert isocitrate to αKG via oxidative decarboxylation (Figure 1). IDH2 and IDH3 are located in the...