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REVIEW ARTICLE – THORACIC ONCOLOGY

Landmark Trials in the Surgical Management of Mesothelioma

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ABSTRACT The treatment of mesothelioma has evolved slowly over the last 20 years. While surgery as a standalone treatment has fallen out of favor, the importance of multimodality treatment consisting of combinations of chemotherapy, radiotherapy, and surgery have become more common in operable, fit patients. In this review, we discuss trials in surgery, chemotherapy, and radiation that have shaped contemporary multimodality treatment of this difficult malignancy, and we touch on the new and emerging immunotherapeutic and targeted agents that may change the future treatment of this disease. We also review the multimodality treatment regimens, with particular attention to trimodality therapy and neoadjuvant hemithoracic radiation strategies.

Mesothelioma is a rare primary malignancy of the pleura. Most cases are related to asbestos exposure that commonly occurs as an occupational hazard of certain professions, as in the case of asbestos miners, demolition workers, pipefitters, shipyard workers, and brake padding factory workers, among others. Due to the long latency period of approximately 20–50 years, with an average of an estimated 40 years, incident cases remain attributable to remote prior exposure.[1] As occupational and environmental health regulations regarding asbestos were not introduced until the 1970s, and further expanded in the 1980s, the incidence of this disease may have yet to peak. Although its production was halted in the US in 2002, asbestos is still produced and used globally. In Canada, for instance, asbestos mining in the eastern township areas of the province of Quebec, and subsequent exports to China and India, persisted until 2012 and was only recently banned as of 2018.[2]

Although rare, mesothelioma has a poor prognosis despite aggressive treatment. According to the American Cancer Society, the 5-year survival rate is under 10% for all disease stages, and approximately 2000–3000 people die in the US every year,[3] with about 40,000 deaths per year worldwide.[4] The median overall survival of patients with surgically respectable disease is about 12 months.[5,6] Outcomes are related to stage at disease presentation, functional status, and response to chemotherapy.[7,8] Tumor details such as number of tumor sites and tumor volume have also been shown to be prognostic,[9] and recently the nodal classification was revised such that ipsilateral mediastinal nodal disease was reclassified as N1 disease. The main difficulty in surgical therapy of the disease is a function of the pleural anatomy—it is very difficult to respect the pleura with a true microscopically negative margin. Furthermore, this anatomy makes resection potentially compromised, with high rates of recurrence.[5,10]

A wide range of treatment strategies are now in use. Treatment modalities include surgery, radiation, chemotherapy, emerging immunotherapies, and multimodality regimens. In this article, we review the landmark trials, both randomized and non-randomized, regarding the use of chemotherapy in advanced disease, the role of surgery in the treatment of mesothelioma, and the controversies regarding the extent of appropriate surgical resection, intraoperative adjuncts to be used in concert with surgical resection, and various multimodality combinations, in particular the use of neoadjuvant hemithoracic radiation and surgery. Finally, we discuss new and emerging therapies, such as immunotherapy, that may offer improvement outcomes in the future.

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CHEMOTHERAPY: THE ONLY PROVEN TREATMENT

Currently, the only proven therapy to increase survival in malignant pleural mesothelioma of any stage is chemotherapy. Up until the early 2000s, no treatment had been shown to convincingly lengthen survival for patients with mesothelioma in randomized trials. However, in 2003, Vogelzang et al. published the first data to support a treatment regimen in mesothelioma that prolongs overall survival. They compared premetrexed plus either cisplatin or carboplatin with a platinum-based monotherapy.[6] The platinum arm of the study was selected because it was the only known active agent in mesothelioma at the time. The trial was positive for the primary endpoint of overall survival and for additional endpoints of progression-free survival and pulmonary function. The study demonstrated that median survival with the combined drug regimen was 12.1 months versus 9.3 months for platinum monotherapy. Subsequently this combination of therapeutic agents has been shown to increase progression-free survival and increase overall survival when compared with platinum-based therapy alone.[6,11–13] Bevacizumab has also been studied in the MAPS randomized trial comparing premetrexed plus cisplatin with or without bevacizumab. This trial demonstrated that the addition of bevacizumab to gold-standard therapy produced a longer median overall survival of 18.8 months versus 16.1 months, and progression-free survival of 9.2 months versus 7.3 months.[14] In combination, these trials demonstrated that treatment could lead to improvements in survival, however modest, and these chemotherapy regimens remain the cornerstone of treatment for pleural mesothelioma in the present day.

THE ROLE OF SURGERY: THE MARS, MARS2, AND MESOVATS TRIALS

The role of surgery for malignant pleural mesothelioma has been a topic of debate for decades. While the oncologic principle of a microscopically negative surgical margin with no residual disease still applies in the case of mesothelioma, the anatomy of the pleura makes this a practical and technical challenge. Thus, the goal of resection with malignant pleural mesothelioma is to obtain a macroscopic complete resection (MCR) with as little residual tumor as possible, typically defined as <1 cm of disease or no visible residual disease. An extrapleural pneumonectomy (EPP) involves the resection of the lung with its associated visceral pleura, as well as the hemidiaphragm, pericardium and remaining parietal pleura. Subsequently, lung-sparing options were developed, such as gross disease removal via pleurectomy and decortication (P/D).[15] The Achilles heel of any cancer operation is local recurrence, and despite even maximal surgical resection via EPP with MCR, there is a high rate of recurrence after surgical resection, approaching 40% in some series.[10] At present, maximal surgical cytoreduction is recommended for patients with early-stage disease who can tolerate a surgical operation.[5] However, patient selection is of utmost importance to minimize morbidity and should only be offered to those who meet specific criteria regarding preoperative cardiopulmonary function, and stage and extent of disease. Epithelioid histology has been most strongly associated with superior survival outcomes after surgery in retrospective series.[16] Non-epithelioid histology has been associated with poor prognosis, and many programs do not offer these patients a surgical option, although there is some evidence that biphasic patients may be suitable operative candidates. Figure 1 compares EPP to P/D.[17–19]

The choice of surgical therapy is another controversial area in the treatment of mesothelioma. Some programs offer lung-sparing surgery to patients who have disease confined to the pleura, typically non-fissural, and without ipsilateral lung nodules, because these operations tend to be less morbid than EPP. In a recent systematic review comparing morbidity and mortality of P/D and EPP, perioperative morbidity and mortality were significantly lower in the P/D group (2.9% vs. 6.8% mortality; 27.9% vs. 62% morbidity).[20] In a separate review, data from the STS database compared major morbidity after EPP versus P/D, defined as acute respiratory distress syndrome, reintubation, reoperation, and sepsis.[21] P/D had less frequent major morbidity perioperatively than EPP (3.8% vs. 24.2%). In addition, it highlighted that mortality for EPP was higher when performed in low-volume institutions compared with high-volume centers. Overall, mortality was also significantly lower (3.1% vs. 10.5%) for P/D versus EPP.[21–24] The retrospective nature of these data and the inherent selection biases for patients with less bulky disease make these results difficult to interpret, although there is general consensus that in fact P/D is a less morbid option for certain eligible patients and may in fact lead to similar outcomes.

Until recently, there were no completed randomized clinical trials comparing surgery with no surgery for malignant pleural mesothelioma in patients undergoing multimodality therapy. One such study is the MARS trial published in 2011, which compares EPP with no EPP in patients with mesothelioma who are surgical candidates.[25] The MARS2 trial, a similar study but assessing the outcomes of P/D rather than EPP, is currently recruiting.[26]

Extrapleural Pneumonectomy (EPP)		Pleurectomy and Decortication (P/D)
- En bloc resection of lung, pleura, pericardium - Allows for macroscopic complete resection (R1) with a theorectically improved disease clearance - Unable to perform in patients with poor cardiopulmonary reserve		- Removal of parietal and visceral pleura w/sparing of lung parenchyma - Allows for macroscopic complete resection (R1) - Unable to perform in patients with bulky, fissural, or invasive disease into the lung parenchyma
✓	More complete resection for intrafissural and intraparenchymal disease	
✓	Tolerance of adjuvant hemithoracic radiation (decreased risk of pneumonitis)	
✓	Disease-free Survival	
=	Overall Survival	=
=	Risk of recurrence	=
	Morbidity and Mortality (Perioperative)	✓
	Quality of Life	✓
	Cardiopulmonary reserve	✓
	Tolerance of adjuvant therapies for recurrence	✓

FIG. 1 Comparison of extrapleural pneumonectomy versus pleurectomy and decortication for the management of malignant pleural mesothelioma

The MARS and MARS2 Trials

The MARS trial, reported in 2011, compared patients with mesothelioma without mediastinal lymph node involvement and/or distant disease after they were randomized between EPP and no EPP in the context of trimodality therapy, consisting of neoadjuvant chemotherapy and adjuvant radiation. In this trial, 50 patients were randomly selected to EPP ($n = 24$) versus no EPP ($n = 26$). Patients underwent three cycles of chemotherapy with subsequent computed tomography (CT) staging to evaluate the progression of disease. Patients without evidence of unresectable disease or distant metastases and whom were deemed fit enough to undergo surgery were then evaluated by a multidisciplinary team to determine candidacy for enrollment. They were then randomized to EPP followed by radical radiotherapy versus no EPP. The trial was originally designed as a feasibility trial, but it failed to meet its primary endpoint of enrolling 50 patients in 1 year.[27]

Despite this, the MARS authors reported clinical endpoints, including completion of trimodality therapy, perioperative mortality, quality of life (QoL), overall survival, progression- or relapse-free survival, and death from any cause. Of the 24 patients selected to EPP, 19 operations were attempted and 16 had a completed surgical operation. Only 8 of the 16 patients who underwent surgery received radical radiotherapy (33.3% completion of trimodality therapy). There were three perioperative deaths (15.8%) and, of the 16 who had completed operations, there was at least one postoperative complication in 11 patients (68.8%). One patient in the no-surgery group died after receiving EPP outside of the trial. When comparing survival, 52.2% of the EPP group were alive at 12 months, compared with 73.1% in the no-EPP group. The adjusted hazard ratio for prespecified prognostic factors was 2.75 (1.21–6.26, $p = 0.016$). Median survival was 14.4 months for EPP and 19.5 months for no EPP. There were no statistically significant differences in QoL scores. The authors concluded that the data suggested that radical surgery in the form of EPP offers no therapeutic benefit and may in fact harm patients.

However, the trial must be interpreted in light of several important shortcomings, and the conclusion that EPP is not beneficial has been viewed as an overreach not supported by the data.[28] First, the study was significantly underpowered for many of the endpoints evaluated in the study, with less than 10% of the *a priori* calculated sample size, and the trial design was that of a feasibility trial, not one intended to compare outcomes. There was also poor protocol compliance—6 of the 26 patients in the non-EPP group ending up undergoing off-protocol surgery (three EPP and three non-EPP patients) and only 16 of the 24 patients in the EPP group underwent a successful operation. The chemotherapy regimen has also been drawn into question as it was not standardized across the study participants, nor was the timing of surgery in relation to initiation of chemotherapy. In addition, the perioperative

mortality rates were far higher in the MARS trial (18%) than has been seen in other retrospective and prospective studies (ranging from 0 to 5%).[29–34] While the results force us to question the value of surgery, the trial has significant limitations, and any conclusions on the clinic endpoints can only be viewed as speculative. Many surgeons still believe that the superior disease clearance and cytoreduction afforded by EPP is of value in highly selected patients. Importantly, it allows for the hemithorax to be treated aggressively with high-dose radiation therapy postoperatively with no risk for ipsilateral pneumonitis. Finally, despite the high risk of morbidity and mortality associated with the operation, there have been numerous studies suggesting a possible, but not clear, improvement in survival in select patient populations who undergo EPP, especially in high-volume centers.[35–38]

The MARS 2 trial is currently accruing and will aim to assess similar primary and secondary outcomes of the original MARS trial, but for extended P/D rather than EPP. Choice of surgical approach is a matter of controversy, with many surgeons advocating for a less radical approach than an EPP. In addition to minimizing morbidity, there may be an advantage in terms of better tolerance of additional therapy when a recurrence occurs.[39–41] The study began enrolling in 2015, with an estimated completion date of 2022. The aim of the study will be to assess survival, progression-free survival, QoL, and serious adverse events of radical surgery in the form of extended P/D with trimodality therapy compared with chemotherapy alone.[26] There is hope the results will complement those of the MARS study and suggest P/D as a better alternative to EPP in terms of equivalent disease control with a better morbidity profile.[42]

Surgical Palliation

While the role of surgery in curative therapy for mesothelioma is debated, surgery has an undoubted role in palliation of mesothelioma. Patients with advanced, surgically un-respectable disease and, most commonly, symptomatic pleural effusions are considered for palliation via a variety of surgical approaches. Chronic air leaks and recurrent pneumothorax may also need surgical palliation. This can take the form of decortication and pleurodesis, most commonly via talc, or placement of indwelling catheters.[43–49] In the MesoVATS trial, patients were randomly assigned to talc pleurodesis versus partial pleurectomy. While overall 1-year survival was equivalent between the two groups, surgical and respiratory complications as well as median hospital stay were increased in patients who underwent video-assisted thoracopic surgery (VATS) pleurectomy.[50] Talc pleurodesis and/or placement of a tunneled catheter are generally preferred at most institutions for these reasons. For patients with pericardial effusions, a pericardiocentesis or creation of a sub-xiphoid window may improve symptoms and allow patients to tolerate additional therapies.[51–54] Regardless of which palliative measure is selected, great care must be taken when performing these procedures as mesothelioma is well-known to seed operative and procedural sites with metastases. Subcutaneous tunneling of indwelling catheters is a well-known seeding site for mesothelioma.[55]

MULTIMODALITY THERAPY: TRIMODALITY, ADJUVANT RADIATION, AND SMART

In the modern era, multimodality treatment has become the standard of care for operable mesothelioma in fit patients. While systematic reviews have suggested overall improved survival rates ranging from 13 to 29 months for patients undergoing trimodality therapy,[56] and survival as high as 20.8–59 months in those able to complete trimodality therapy,[34,57,59] the optimal sequence and combination of chemotherapy, radiation, and surgery remains controversial.[5]

Trimodality Treatment: The Sloan-Kettering Protocol

Trimodality treatment, most commonly in the form of neoadjuvant chemotherapy, surgical resection and adjuvant radiation, has emerged as the preferred approach for operable, fit patients with localized disease in many centers. This treatment concept was pioneered by Valerie Rusch and her team at Memorial Sloan Kettering Cancer Center in New York.[33] Although it was not randomized, they conducted a prospective feasibility and efficacy trial in which eligible patients underwent neoadjuvant chemotherapy, surgical resection with EPP, followed by external beam radiation therapy to the ipsilateral hemithorax. Patients included were stage T1-3 N0-2 M0 and were physiologically fit. All patients underwent EPP 3–8 weeks after chemotherapy was completed, followed by radiation therapy 4–12 weeks after surgery. Of the original 72 patients who began chemotherapy, 40 patients completed the trimodality therapy regimen. Overall survival for the groups was 29.1 months for those who completed RT, 21.9 months for patients who completed EPP, and 16.8 months for the intention-to-treat (ITT) population. One-year survival was 65.2% in the ITT population compared with 90% in the patients who completed treatment, with 2-year survival of 37.2% and 61.2%, respectively. Of all the patients who underwent EPP, 40% had recurrent disease, with median time to relapse of 18.3 months. Relapse-free rates were 63.8% at 1 year and 38.9% at 2 years. Surgical mortality was 3.7% in the study, with one

patient dying from radiation pneumonitis secondary to intensity-modulated radiation therapy (IMRT).

This approach demonstrated that while trimodality may be difficult to tolerate for some patients, long-term, disease-free remission and improved survival can be achieved with aggressive treatment for those able to tolerate treatment. However, local and distant relapse continues to be a significant limitation. This points to the need for better systemic treatment and highlights the difficulty in obtaining an R-margin. Notably, prolonged survival was only achieved in patients who could tolerate all the elements of therapy, reinforcing the importance of patient selection, especially with the high morbidity and mortality associated with EPP.

The Role of Adjuvant Radiation: The SAKK Trial

Given the significant difficulties that certain groups of patients experience with trimodality therapy, many investigators have focused on evaluating the component treatments to maximize benefit and minimize toxicity. Adjuvant radiation has been suggested to decrease locoregional recurrence and improve survival.[33,59] Studies assessing the effects of conformal radiation therapy (CRT) as well as IMRT have been shown to result in improved locoregional control (40–71%) and 2-year overall survival (18–57%) in multiple studies.[57,60–63] However, radiation is associated with risks such as pneumonitis, hence trials were developed to evaluate adjuvant radiation after surgery for mesothelioma.

The SAKK 17/04 trial was a two-phase, randomized trial to assess the effects of adjuvant hemithoracic radiation after EPP.[58] Prospective studies have shown neoadjuvant chemotherapy in combination with EPP and various forms of postoperative radiation therapy to have a median overall survival of 15.5–19.8 months, suggesting improved survival compared with chemotherapy and surgery alone.[30,33,34,64] Fit patients with respectable, clinical stage T1-3 N0-2 M0 disease were administered neoadjuvant chemotherapy and underwent EPP. Those who had a complete macroscopic resection (CMR, i.e. R0 or R1) were then randomized to hemithoracic radiation or no radiation. In total, 151 patients completed chemotherapy, with 125 patients who underwent surgery, of whom 96% achieved R0 or R1 resections. Five patients died within 30 days of operation (4%) compared with the 18% reported in the MARS trial, with five additional deaths at 60 days (8%). Median overall survival of the 151 patients in part 1 was 15 months and median progression-free survival was 8.6 months.

Radiotherapy was then initiated within 10 weeks of surgery. Ninety-nine patients in total were assessed for inclusion in part 2, three of whom were found to not have CMR. Fifty-four of the 96 remaining patients (56%) were deemed eligible for radiotherapy and were randomized. QoL was worse in the radiotherapy group, as were activity scores up to 4 weeks after randomization. Although overall well tolerated, 46% of patients receiving radiation developed grade 3–5 toxicity. Median relapse-free survival was 5.7 months (3.5–8.8 months) in the no-radiotherapy group and 7.6 months (5.2–10.6 months) in the radiotherapy group. Median overall survival for all 151 patients was 15.0 months, and 20.8 months (14.4–27.8 months) in the no-radiotherapy group and 19.3 months (14.2–21.2 months) in the radiotherapy group.

Overall, the results of this study do not support the use of hemithoracic radiation therapy after neoadjuvant chemotherapy followed by EPP. There may be some benefit with radiation therapy for progression-free survival, although this was not shown to be statistically significant. There were no benefits on median survival, and the radiotherapy group actually had lower overall survival and decreased QoL scores, although, again, these were not statistically significant. Thus, there was an increase in treatment burden as well as a risk of adverse effects, with no effect on the outcome of disease for patients who received radiotherapy.

These results underscore the fact that trimodality therapy requires careful patient selection. Echoing the results of the MARS trial, the SAKK trial showed that in combination regimens, adjuvant radiation seemed to add little in terms of survival benefit, at the cost of significant toxicity and worsened QoL. One criticism of the SAKK trial is that a small number of patients were inappropriately treated with their adjuvant radiation protocols. As a response, the IMPRINT trial is now underway, with the intention of randomizing P/D patients to no radiation versus IMRT.[65] Radiation undoubtedly has some role to play in multimodality treatment, especially in reducing local recurrence, however treating clinicians also need to be cognizant of treatment-related morbidity and select therapies judiciously in this already very frail population. Further trials evaluating the role of P/D in combination regimens may also shed some light on the best combination regimens, including those that use adjuvant radiation, such as the IMPRINT trial noted above.

Another application for adjuvant radiation is its use in port and tract site irradiation as a prophylactic measure for preventing tract site metastases. Mesothelioma is known to seed intervention sites, and for patients in whom a diagnosis of mesothelioma is made after diagnostic pleuroscopy, for example, it has long been held that port sites should be irradiated. In a randomized control trial, Bayman et al. showed that prophylactic radiation to interventional sites did not decrease the occurrence rate of chest wall recurrences.[66] No significant difference was seen in

the incidence of chest wall metastases at 6 months between the prophylactic radiotherapy and no-radiotherapy groups (3.2% vs. 5.3%; odds ratio 0.60, 95% confidence interval 0.17–1.86). Skin toxicity was the most common adverse effect, with most patients developing minor grade 1 or 2 toxicity. This study concluded that there was no role for routine use of prophylactic irradiation of intervention sites. Although some differences were noted beyond the 1-year mark, the study did not have enough power to investigate beyond the 6-month timeframe. At this time, neither the European nor American Society of Clinical Oncology (ASCO) guidelines recommend routine prophylactic radiation for the prevention of port or tract site metastases.

THE ROLE OF NEOADJUVANT RADIATION: THE SMART TRIAL

Despite aggressive multimodality treatment with trimodality protocols, local recurrence remains a major problem after surgery for mesothelioma. One technical issue is that obtaining a negative margin and preventing the local spread and complete tumor removal during resection surgery for mesothelioma is an anatomical challenge. Hence, a strategy whereby radiation could be delivered upfront would be advantageous to 'sterilize the margins', as has been proposed for other cancer types such as rectal cancer and retroperitoneal sarcoma with similar margin issues.[67,68] Therefore, the SMART (Surgery for Mesothelioma after Radiation Therapy) trial was devised.

The SMART trial assessed outcomes of patients with respectable disease who underwent neoadjuvant hemithoracic radiation followed by EPP 1-week post-RT.[69] Doses of 25 Gy administered in five daily fractions over 1 week with a boost of 5 Gy to areas of gross disease and tumor tract sites were administered to patients using multibeam IMRT. Eligible patients (T1-3 N0 M0 disease, able to tolerate multimodality therapy) then underwent EPP within 5 days (to pre-empt the onset of pneumonitis). Adjuvant chemotherapy was reserved for pathology confirmed pN2-positive patients. In total, 25 patients were able to complete IMRT and EPP. No grade 3–5 toxicities were reported after radiation, with the most common complaints being fatigue, nausea, and esophagitis. There were no deaths within the 30-day perioperative period, with one death from a treatment-related complication (empyema) at 88 days. Fifty-two percent of patients developed grade 3+ complications after surgery, most commonly atrial fibrillation. There were no incidences of bronchopleural fistula despite the neoadjuvant radiation therapy. Thirteen patients had pN2 disease and five (38%) underwent adjuvant chemotherapy.

The results from this study were encouraging. Patients in the study reached a median follow-up of 23 months, with cumulative overall survival of 58% at 3 years. Perhaps, most significantly, the epithelioid subtype had a cumulative survival of 84% and disease-free survival of 65% at 3 years. This may suggest the epithelioid subtype to be more prone to radiation effects than other subtypes. Eleven of 25 patients in total developed recurrence, and for patients with epithelial subtype and N2-negative disease, only one (11%) developed recurrence.

The results of the SMART trial suggest patients with early disease, no lymph node involvement, and particularly patients with the epithelial subtype may have significantly longer survival with neoadjuvant radiation, EPP, with or without adjuvant chemotherapy. There were minimal adverse effects from the radiation therapy used in this study. Expectedly, there was significant morbidity with EPP, however, compared with previous studies such as the MARS trial, perioperative mortality was low, with only one operative-related death. This may be perhaps due to patient selection as well as timing of treatment, as these patients had earlier-stage disease and did not undergo neoadjuvant chemotherapy. This further underscores the importance of having multidisciplinary coordination among experienced radiation oncologists, medical oncologists, and thoracic surgeons in the multimodality treatment therapies of MPM.

There are several drawbacks to the SMART protocol that must be considered. First, once the hemithoracic radiation has been delivered, the lung must be removed before severe pneumonitis sets in. Additionally, if the tumor is determined to be unresectable at operation, the lung must be resected anyway to prevent pneumonitis (an R2 resection). Furthermore, Dr. Cho and colleagues report minimal morbidity,[69] the radiation may have effects on QoL or long-term morbidity not captured in their data. Without a doubt, more patients need to be enrolled in this protocol to test its generalizability, however the SMART trial has shown a promising treatment for patients with early stage, resectable, epithelial mesothelioma.

INTRAOPERATIVE ADJUNCTS: INTRAPLEURAL CHEMOTHERAPY AND PHOTODYNAMIC THERAPY

Novel intraoperative therapies for malignant pleural mesothelioma include heated intraoperative chemotherapy (HIOC) and intraoperative photodynamic therapy (PDT).[70] The aim of these therapies is to target microscopic metastatic disease and improve locoregional control of tumor progression. These strategies are aimed at reducing local recurrence and have the added advantage of theoretically

TABLE 1 Checkpoint inhibitor trials in pleural mesothelioma[86]

Therapeutic agent	ClinicalTrials identifier	Target
Nivolumab/Ipilimumab	NCT03918252	Anti-PD-1/anti-CTLA4
Atezolizumab	NCT03228537	Anti-PD-L1
Pembrolizumab	NCT02707666	Anti-PD-1
Pembrolizumab	NCT02959463	Anti-PD-1
Tremelimumab/durvalumab	NCT02592551	Anti-CTLA-4/anti-PD-L1

better toxicity profiles compared with systemic therapies. HIOC has been in use since the 1980s and is used for multiple abdominal cancer operations (referred to as hyperthermic intraperitoneal chemotherapy [HIPEC] in the abdomen).[71,72] It has been associated with longer survival and lower local recurrence rates in retrospective analyses in patients receiving chemotherapy and surgery, and for patients with N1/N2 disease;[73] however, it has not been associated with prolonged survival if patients received trimodality therapy, perhaps due to the similar effect of adjuvant radiation on locoregional control.[70] Thus, for patients who may be unable to undergo adjuvant radiation, HIOC may be a suitable alternative to obtain local control. PDT consists of giving patients a photosensitizing agent followed by activation of that agent with specific wavelengths of light, producing oxygen species that cause cellular destruction and necrosis.[74] Depth of penetration is an advantage as it typically penetrates several millimeters, thereby potentially reaching microscopic tumor while also preventing damage to underlying lung parenchyma. Results have been encouraging, but generally follow a similar pattern as for other treatment modalities—patients with complete macroscopic resection and epithelial histology tend to do well. There may be a possible immunostimulatory effect of PDT causing an activation of an anti-tumor response, especially with the epithelial histologic subtype.[75–77] A randomized control trial is currently ongoing to assess the effects of P/D and PDT in combination.[78] Whether this strategy will be able to extend P/D to additional patients, such as those with fissure or bulky disease who would not typically be P/D candidates, remains to be seen.

TARGETED THERAPY AND IMMUNOTHERAPY

Recent advances in immunotherapy have revolutionized the oncology landscape, and immunotherapy and targeted treatments have held out much hope for mesothelioma. One large recent phase III trial, the Lume-Meso trial, examined nintendinib, a targeted PDGF/VEGF/FGF inhibitor. Unfortunately, the investigators were not able to demonstrate a progression-free survival difference for patients receiving nintendinib.[79] Similarly, the DETERMINE trial studying tremelimumab, a CTLA-4 inhibitor, failed to show an increase in overall survival compared with placebo in patients with advanced malignant mesothelioma.[80] Checkpoint inhibitors have begun to be tested in the neoadjuvant, first-line, and salvage settings. The DREAM trial was a promising non-randomized trial of durvalumab in the first-line setting, with 65% 1-year overall survival; this will hopefully be translated into a phase III trial.[81] Checkmate-743 is another trial evaluating nivolumab in combination with ipilimumab versus combination chemotherapy.[82,83] Interim results have met the primary endpoint for overall survival and show improved outcomes compared with standard chemotherapy regimens. Median overall survival was 18 months compared with 14 months when compared against carboplatin or cisplatin with premetrexed.[84] This led to US FDA approval in October 2020 for its use in unresectable malignant pleural mesothelioma.[85] Further results are yet to be reported. Ongoing clinical trials involving checkpoint inhibitors in combination with surgery are shown in Table 1.[86]

CONCLUSIONS

Mesothelioma remains a difficult disease to treat, with poor outcomes, despite aggressive therapy. While new immunotherapeutic and targeted agents may change the landscape of treatment, surgery remains a cornerstone of therapy. Trials in the treatment of mesothelioma have established chemotherapy as the backbone of treatment in non-surgical patients but have failed to clearly delineate chemotherapy, surgery, radiation, and other modalities, as well as their timeline of implementation, that are of clear benefit to patients. The role and type of surgery remains hotly debated. Multimodality treatment in well-selected patients remains the standard approach. Any patient with mesothelioma should unquestionably be offered treatment at a high-volume institution with experience in treating and palliating the disease. Furthermore, any patient treated for mesothelioma should ideally be treated on a research protocol, given how little we know with certainty about the disease.

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