Perspective

Multimodality therapy for malignant pleural mesothelioma

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To date, it is widely accepted that best long term results after treatment for malignant pleural mesothelioma are achieved when several modalities are combined. However, there is still a debate which combination of treatment in which stage of the disease and for which patient should be recommended and different institutions follow different treatment regimens. If mesothelioma is in a resectable stage, macroscopic complete resection (MCR) - realized as extrapleural pneumonectomy (EPP) or radical pleurectomy/decortication (P/D) - is the basic concept, to be supplemented by chemo- and/or radiotherapy either in a neo-adjuvant or adjuvant combination. Various local therapies during surgery are also applied. Combining EPP with adjuvant chemo-radiotherapy, median overall survival (OS) data are consistently reported to range between 13-23.9 months. Applying chemotherapy as an induction concept (neo-adjuvant chemotherapy) median overall survival is in a comparable range and reaches up to 29.1 months [reviewed in (1)].

We herein discuss the individual modalities of multimodality therapy - surgery, chemotherapy, radiotherapy, as well as other possible modules of a multimodal therapy.

Role of macroscopic complete resection

At the International Mesothelioma Interest Group (IMIG) meeting 2012 in Boston, Valerie Rusch reported a 19-month median survival among 1,359 MPM patients undergoing surgical resection (P/D or EPP) from the IASLC world-wide registry of patients with all stages of epithelial MPM. These data will be published soon. Moreover, patients undergoing EPP for early stage disease had a median survival of 40 months which is not surprisingly superior to other stages. Therefore, based on current literature and the IASLC report, it was concluded by several IMIG members that surgery by either P/D or EPP, with the goal of obtaining a macroscopic complete resection, should be performed in the multimodality treatment of MPM. Furthermore, it was discussed that both types of cytoreductive procedures have their pros and cons and are currently selected on the basis of disease distribution, institutional experience, and surgeon preference and experience. Furthermore, it was collectively agreed that multimodality treatment should be performed in centers of high expertise and by surgeons who have achieved morbidity and mortality rates within the scope of current literature (D. Sugarbaker, V. Rusch, in press).

For the time being, there remains no evidence based answer as to which procedure - P/D or EPP - is the more appropriate technique to achieve long term survival in mesothelioma patients, although the rate of recurrence seems to be increased in patients who underwent P/D (65% in comparison to 33%) (2). Most studies have reported either on EPP or on P/D and if studied together P/D was usually chosen for earlier stages and EPP for more advanced stages. The largest report ever comparing both procedures in a retrospective multicenter study on 663 patients combining the experience of three large centers in the United States concluded that the study emphasizes the similarities in outcome after EPP or P/D (2).

MCR is the basic concept and the technique chosen has to be tailored according to the patient's performance status and wish, stage of disease in terms of possible MCR, and available combination modalities. A clear recommendation which procedure is the most appropriate for early stage I or II mesothelioma patients is missing. Due to a lack of reliable clinical staging, the decision is occasionally taken only in the operating theatre since not in all patients can either procedure can be performed based on imaging modalities only. But there are some unambiguous

situations where P/D is clearly advised: for patients with compromised cardiac or pulmonary function, or with certain co-morbidities, who would not tolerate an EPP without excessive risk. Moreover, a parenchyma-sparing procedure in the sense of debulking P/D might be recommended if all gross tumor cannot be removed macroscopically, especially in stage IV patients (3). It has to be taken into account, that adjuvant radiotherapy cannot be applied safely after P/D, because radiation of the intact lungs results most likely in high rates of pneumonitis, even if modern techniques are applied (4).

EPP has been a matter of recent controversy despite an increasing amount of phase II studies reporting favourable results. Recently the MARS trial concluded prematurely that "EPP within trimodal therapy offers no benefit and possibly harms patients", although only 16 patients were actually treated with EPP (5). The study was not designed to answer the question of benefit or not of EPP but rather of the feasibility of such a trial. A definitive answer to this question would need an accrual of 670 patients to identify a survival benefit (6). Also, their criticism of excessively high morbidity and mortality rate is not supported by recently reported trials for trimodality therapy as described above.

Chemotherapy

Recent reviews (7,8) summarize antifolate pemetrexed and cisplatin to achieve best overall survival and quality of life - therefore cisplatin plus an antifolate is currently the most frequently used regimen for first line chemotherapy in a neo- or adjuvant setting. There is no evidence for the application of chemotherapy before or after surgery but several arguments exist for and against.

Induction chemotherapy

One particular multimodal approach is to sequence surgery following induction chemotherapy - a concept which has been adapted from favourable experience in stage III non-small cell lung cancer with the idea to possibly downstage the tumor for improved radicality (9), which can be achieved between 70% and 84% (10,11) with acceptable response rates of 30-40%. But reports about complete response as observed in other cancers are anecdotal or at least extremely rare. The concept was studied more in detail in a Swiss multi-center trial (9) resulting in a surgical 2.2% mortality rate and a median survival of patients who were intended to treat of 19.8 months and of 23 months for those who completed the trial including EPP. It has been applied since then by many other groups with similar results (10-13). Beside the intended down staging effect, it is generally observed that chemotherapy is better tolerated if applied before surgery, and therefore allows the application of the required full dose because of better patient compliance. Furthermore, tumor aggressiveness may be estimated based on post-chemotherapy CT scans, helping decision-making regarding the proposed surgical procedure and therefore patients may be successfully excluded from ineffective surgery. It was of concern that surgical mortality and morbidity might be increased after chemotherapy. This was not observed in experienced centers, where morbidity ranges between 22% and 82% and mortality between 0% and 11.8% (1), comparable to the numbers reported for patients treated in an adjuvant setting.

Adjuvant chemotherapy

As already mentioned above, there are no clear differences in survival rates regardless if chemotherapy is applied before or after surgery and only a slight trend in favor of neo-adjuvant chemotherapy is observed which is difficult to interpret. Adjuvant chemotherapy has the advantage that a definitive tumor stage is available after surgery for patient selection for chemotherapy. Surgery is not delayed for prior chemotherapy and tumor resection might therefore be easier as the tumor is removed as soon as possible and cannot grow any larger or invade beyond resection limits. A disadvantage of adjuvant chemotherapy is decreased tolerance due to prior surgery and decreased patient performance status, therefore reducing compliance. The starting dosage of chemotherapy might be reduced compared to induction chemotherapy. To add on radiotherapy in this setting seems to be more challenging.

Radiotherapy

Prophylactic RT to prevent tumor cell seeding along thoracocentesis or drainage tracts did not show a significant reduction of the relative risk of tract metastases as assessed in a meta-analysis (14). Radical radiotherapy as part of multimodal therapy has been evaluated for after EPP and P/D. Adjuvant RT in the EPP setting has the major advantage in that the lung is removed, however other critical organs such as the heart, liver, kidneys, and spinal cord, as well as the contralateral lung, are still at risk. The high dose hemi-thoracic intensity-modulated radiation therapy (IMRT)

has been developed to improve precision and reduce toxicity. However, as fatal pneumonitis is a critical side effect, this technique is recommended in clinical trials at specialized centers only (15). Hemi-thoracic radiation after EPP has been evaluated in several studies with good local tumor control in comparison to historical controls (16). Trimodal therapy including induction chemotherapy, EPP, and adjuvant hemi-thoracic radiotherapy reported median survival rates of up to 29 months (10). An ongoing multicenter Swiss trial (SAKK) is currently evaluating in a randomized protocol the value of curative postoperative hemi-thoracic radiotherapy after induction chemotherapy and EPP (17). In a study by Van Schil *et al*., 65% of the patients completed all three steps of the treatment (13). Grade 3-4 toxicity (18) persisted after 90 days in 5.3% of the patients. Median overall survival time was 18.4 months and median progression-free survival 13.9 months. Only 42% of the patients met the definition of success. Curative RT in a P/D setting is definitely limited by the fact that the lungs are still in place and even IMRT technique does not allow treating the disease along the fissures. Dose restrictions have to be accepted in order to decrease the risk of fatal radiation pneumonitis. The loco-regional control rate and survival has so far not been improved by the addition of radical radiotherapy to P/D, causing high associated toxicity, even if performed in experienced centers (19,20). Another aspect to consider is that a complete course of adjuvant radiotherapy is difficult to tolerate for many patients who undergo surgery.

A very new and promising approach is to apply radiation therapy before surgery - in this case - EPP, as an induction radiotherapy concept (presented by Marc de Perrot at the 2012 IMIG International Conference in Boston) (21). Toxicity seems to be acceptable as no NCI Common Toxicity Grade 3 was observed and the survival rates reported are very promising as all patients without nodal disease are alive without recurrence so far with a median follow-up of 11 months. The attractiveness of the concept is that this combined approach is performed within 2 weeks, as radiotherapy is applied within one week and EPP sequenced in the following week, but has to be further evaluated.

Other combinations

Beside the more "conventional" modalities such as chemo- and radiotherapy, the multimodality approach can be stretched into other fields such as photodynamic therapy, an approach first reported by Dr Pass in 1990 (22) and elaborated and further developed since at Penn University (23).

Intracavitary photodynamic therapy (PDT)

Photodynamic therapy is a light-based cancer treatment. Light of a defined wave-length agitates a photosensitizer to produce reactive oxygen, which in turn activates a multitude of tumor-killing cascades. Today's best known mechanisms of PDT are direct cell destruction, hindrance of tumor vascularization, and activation of a tumor directed immune response (24). PDT combined as adjuvant intraoperative treatment after P/D or EPP shows promising survival rates of up to 31 months median overall survival (25-28). A recent update given by Dr. Friedberg during the 2012 IMIG International Conference in Boston reported impressive survival dates for PDT after P/D with a median overall survival of 58 months for patients with epithelioid histotype and N0 disease. However similar subgroup analysis has been reported by other groups as well in EPP and chemotherapy.

Intracavitary chemotherapy

In order to improve local tumor control, localized treatment is an attractive approach. The pleura with its large surface is easily accessible and therefore ideal for any localized therapy. For example, applying a chemotherapeutic agent directly to the pleura instead of intravenous treatment has the advantage of achieving higher doses at the required site while reducing systemic side effects. Intracavitary platinum-based chemotherapy performed in both settings (P/D and EPP) was pioneered and refined over the last few decades by MSKCC in New York (29) and Brigham group in Boston (30). Intracavitary chemotherapy is mostly platinum-based regimens conducted intraoperatively following EPP or P/D. To enhance efficiency of the applied chemotherapeutics, they are often applied under hypothermia (31-38). The maximum tolerated dose can be increased up to 225 mg/m^2 cisplatin in comparison to the 100 mg/m^2 applied in intravenous regimens (32). Even in advanced stages a median overall survival of up to 18 months (33) can be reached and the median OS can be 35 months in selected groups (presented at IMIG 2012 by D. Sugarbaker). The treatment related morbidity of 13-65% (37,39) and a mortality of up to a maximum of 29% (36) are based mainly on renal complications which can be attributed to fast absorption and high systemic levels

of cisplatin. Several adjuvant substances can be applied to reduce renal toxicity, such as amifostine, which reduces renal toxicity from 8.7% to 3.7% (34). We have shown in a number of preclinical testings that the pharmacokinetics of cisplatin can be importantly maximized if combined to a fibrin-carrier which is applied on the resected surface of the pleura (40-42). With dosages of 24 mg/m^2, the efficacy was comparable to cisplatin applied as a solution in a dosage of 100 mg/m^2 in terms of loco-regional tumor control, with higher local and significantly lower systemic cisplatin concentrations. Intracavitary chemotherapy with cisplatin-fibrin after P/D is currently being evaluated in a Phase I/IIa clinical study (43).

Selection algorithm and perspectives

The challenge nowadays is therefore more in selecting the right patient for the procedure and a therapy that he benefits the most from. Patients with histologically proven mesothelioma and resectable tumor load who could tolerate the different treatment modalities (including surgery) should be considered for a multimodal approach and be included in a trial whenever possible. The clinical staging and functional assessment is mandatory as a basis for this discussion. In many centers only patients with epithelioid type of MPM and without N2 lymph node metastases are considered as candidates. However, we proposed that N2 nodes in MPM are "local" nodes and therefore should not be an exclusion factor per se. Data about the role of mediastinal lymph node involvement of the different case series are conflicting (9,12) but the results of the new IASLC/IMIG staging project analyzing the largest set of MPM data demonstrate that N2 disease is not a factor which influences survival significantly as compared to the N1 nodes (Rusch *et al*. in press). Furthermore the volume of the tumor is an essential factor for the patient's prognosis (44,45). The final analysis of extended selection algorithms is pending. In order to improve the selection process, the updated IASLC/IMIG staging system, for example considering the different biological performance of the different MPM histotypes, is awaited. Future clinical MPM research should focus on improvement of clinical staging methods and new or refined therapy approaches to attack the problem of local tumor control. With mesothelioma being a rare disease, the number of patients is limited and more innovative trial designs [such as multi-arm multi-stage trials (46)] using cooperative platforms to eliminate less effective treatments may be the best way forward.

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